4

Magnetic Properties of Biological Material

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CONTENTS

4.1 Introduction

Magnetism arises from the movement of electrical charges, such as the oscillation of electrons in a conducting wire, the flow of ions in an organism or the orbital, and spin motions of electrons in an atom. Since all materials contain moving subatomic particles (electrons and protons), all materials are, in some sense, ''magnetic.'' In order to understand more about the role of magnetic materials in organisms, it is first necessary to examine what is meant by the various types of magnetic behavior of materials.

The magnetic properties of materials are dominated by the electron spin motion. In quantum mechanical terms, electrons may assume two possible spin states: spin $+1/2$ or spin $-1/2$. These may also be referred to as ''spin up'' and ''spin down.'' The Pauli exclusion principle states that no two electrons may occupy the same energy state in an atom. This means that no two electrons may have the same set of values for the quantum numbers as they would then be indistinguishable. As electrons are added, they fill up each possible state in a given shell before filling the shell associated with the next higher energy state. The filling of the shells is governed by Schrödinger's wave equation and the quantum numbers.

Electrons are added to subshells in parallel spin configurations first according to Hund's rule. If all electrons are paired, there is no ''spin'' magnetic moment. These materials are still magnetic though, because of the electron's orbital motion. In most materials of biological origin, however, electron spin motion is cancelled, allowing electron orbital motion to dominate.

The spin structure of the transition series elements (iron in particular) is most important for the magnetic properties of biological materials. This is due to the presence of uncompensated spins in the 3d orbital, which gives rise to a spin magnetic moment. The spin moment is much stronger than the orbital moment and is aligned parallel to an applied field.

All materials, including biological materials, fall into one of the three categories of magnetic materials based on the spin and orbital motion of electrons: (1) diamagnetic, (2) paramagnetic, and (3) ferromagnetic.

4.2 Diamagnetic Materials

Diamagnets are materials in which all electron spins are paired (i.e., there are no uncompensated spins). Therefore, the magnetic properties of diamagnets are determined by the electron orbital motion.

According to Faraday's law, in the presence of an applied magnetic field there is an electric field induced that is acting on the orbiting electron. The induced electric field produces a torque on the electron, which gives the electron extra angular momentum. This extra angular momentum produces a magnetic moment, the sign of which is negative (i.e., antiparallel to the induced or applied magnetic field). Therefore, diamagnetic materials are repelled in magnetic fields (they have weak, negative magnetic susceptibility).

4.3 Paramagnetic Materials

Paramagnetic materials are those in which individual atoms, ions, or molecules have some number of uncompensated spins and thus a permanent net spin magnetic moment. As we have stated before, the spin moment is much larger than the orbital moment, so we would therefore expect that the behavior of paramagnetic materials when placed in a magnetic field will be governed by the behavior of the spin magnetic moments. This is indeed the case.

When paramagnetic substances are placed in an external magnetic field, the uncompensated spin moments tend to align, to some degree, parallel to the applied field direction (Figure 4.1). The magnetic energies involved in this alignment are relatively

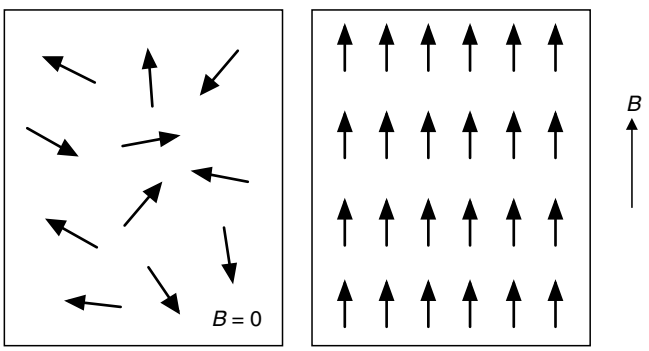

FIGURE 4.1
Orientation of spins in a paramagnet in the absence of a magnetic field ($B = 0$; left) and in the presence of a strong magnetic field (right)

small, and the energy associated with thermal agitation tends to work against the alignment, having a randomizing effect. The degree of alignment of the uncompensated spins with the applied magnetic field depends, therefore, on the strength of the field (the stronger the field, the greater the degree of alignment up to very high fields) and the temperature (the hotter the material, the lower the degree of alignment in the same applied field).

Since the spin moments in paramagnetic materials align with the applied field in this classical model, they add to it, so that the net effect is that these materials are attracted to a magnetic field (and they have a positive magnetic susceptibility). The linear temperature dependence of the magnetic susceptibility in paramagnetic materials was worked out by Pierre Curie and is known as Curie's law:

$$M/H = \chi = C/T$$

where M is the magnetization, H is the applied magnetic field, χ is the magnetic susceptibility, T is the temperature, and C is the Curie constant and is related to the magnetic properties of the material.

In paramagnetic materials, the individual dipole spin moments of the ions may be thought of as noninteracting (in other words, the magnetic moment of one atom has no effect on its neighboring atoms in the material). Because of the noninteraction of the magnetic moments, this fairly weak effect (paramagnetism) is lost upon removal of the external field. Therefore, when a paramagnetic material is not in an external magnetic field, the net magnetic moment in the material is zero because of the randomizing effects of thermal agitation.

4.4 Ferromagnetic Materials

As in paramagnets, in ferromagnetic materials, there are also uncompensated spins; however, these spins are coupled, giving rise to strong magnetic effects. Ferromagnetism may be thought of as a ''group phenomenon,'' where groups of spin moments act in concert, whereas paramagnetism may be thought of as an ''individual phenomenon,'' where the moment of one atom has little or no effect on the moment of neighboring atoms.

In ferromagnetic materials, as in paramagnets, the magnetic susceptibility is positive, and these materials acquire a positive magnetization when placed in an applied field because of alignment of the spin moments in the material with the field. Unlike paramagnets, however, the net magnetization is not lost upon removal of the field (as long as the material is below a certain temperature, which will be discussed in a moment), and the induced moment in the material may be very strong (Figure 4.2). This is to say that ferromagnetic materials exhibit ''hysteresis.''

The mechanism responsible for coupling of the spin magnetic moments in neighboring atoms in a material is due to quantum mechanical phenomena and is governed by the Pauli exclusion principle. The uncompensated spins in individual atoms of a ferromagnetic material may couple either directly (direct exchange) or through an intermediate anion—usually oxygen (superexchange). In ferromagnetic materials, this gives rise to a net magnetic moment because of the coupling of spins in a preferred orientation. Keep in mind that this coupling is quantum mechanical in nature and not purely due to magnetic forces acting between uncompensated spins in neighboring atoms.

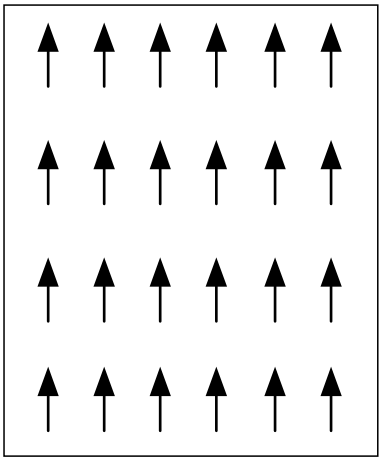

FIGURE 4.2
In ferromagnets, all spins are coupled and aligned, even in the absence of an applied field. This is the origin of remanent magnetization (i.e., hysteresis) in materials.

There are also special cases of ferromagnetism in which neighboring spins are coupled, but not necessarily in the same direction. We will examine two of these cases, antiferromagnetism and ferrimagnetism, as they are important to biological materials, though there are others.

4.4.1 Antiferromagnetism

For some ferromagnetic materials, the exchange coupling between neighboring lattice elements is such that the spins are aligned opposite to each other. This is called antiferromagnetism, and the exchange coupling arises from super exchange according to the Pauli exclusion principle and Hund's rule (Figure 4.3).

In this case the spin moments will still align themselves to an external applied field, only some will be parallel to the applied field and those exchange coupled to them will be antiparallel. This would normally give rise to a material with no net magnetic moment if for every spin up, it was coupled to a spin down. This is not, however, always the case. In some materials, there is a canted antiferromagnetic spin structure (Figure 4.3) or lattice defects and frustrated surface spins (in very fine particles), which can give rise to a net moment in the absence of an applied field.

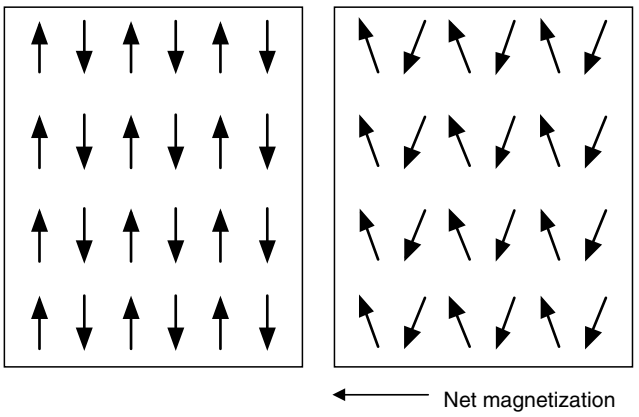

FIGURE 4.3
Pure antiferromagnetic behavior in which spins are coupled antiparallel to each other (left) and an antiferromagnet with a canted spin structure that gives rise to a net magnetization even in the absence of an applied field (right).

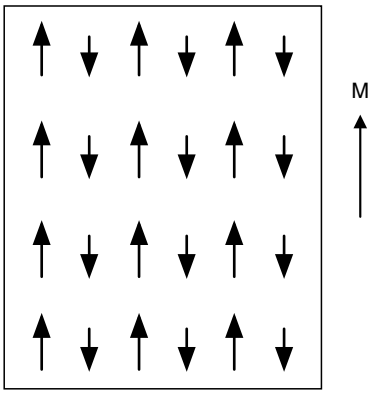

FIGURE 4.4
Electron spin configuration for a ferrimagnet. M = magnetization.

4.4.2 Ferrimagnetism

In addition to antiferromagnetic materials, it is also possible for the neighboring lattice subunits to have unequal numbers of uncompensated electrons coupled antiparallel to each other. This is the case for magnetite (Fe_3O_4), which contains both Fe^{2+} and Fe^{3+} in its lattice structure. The unequal distribution of the two neighboring iron ions gives rise to a net moment (again, even in the absence of an applied field) since one sublattice will have a magnetic moment of greater magnitude than the other, as shown in Figure 4.4. This type of material is called ferrimagnetic.

4.4.3 Temperature Dependence of Ferromagnetism

Since ferromagnetism results from the interaction of atomic moments in materials, there is an exchange energy associated with coupling of the spin moments. At room temperature, this exchange energy is much greater than the energy due to randomizing thermal effects (kT). If thermal energy exceeds the spin coupling (exchange) energy, the coupling breaks down, and the material behaves as a paramagnet. This temperature is dependent on the material and is called the Curie temperature (or, in the case of antiferromagnetic materials, the Néel temperature) (Figure 4.5).

Finally, materials that are superparamagnetic are generally very small (on the order of nanometers), and the electron spins may be coupled either parallel (ferromagnet) or

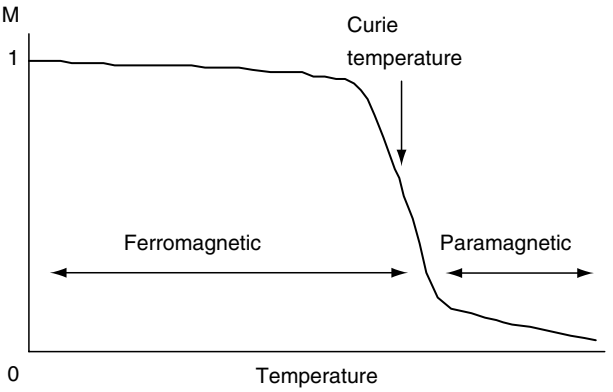

FIGURE 4.5
Magnetization as a function of temperature for a ferromagnet. Above the Curie temperature, spin coupling breaks down, and the material behaves as a paramagnet.

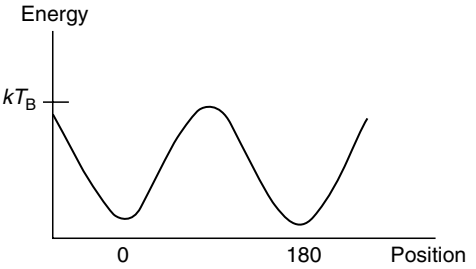

FIGURE 4.6
Schematic of the energy barriers in a superparamagnet. If thermal energy is above a given temperature—the blocking temperature (T_B)—the spins will be able to very rapidly flip between 0° and 180° along the easy axis of magnetization. If the particle becomes larger or the temperature is lowered, the height of the energy barrier constrains the orientation of the electron spins to one or the other of the easy axis energy wells.

antiparallel (ferri- or antiferromagnet). In the case of these materials, however, thermal considerations are dominant. Superparamagnetic materials are named as such because thermal energy causes them to behave—even though this is a special class of ferromagnetism—like a paramagnet. The difference is that, because of coupling of the spin moments, thermal energy causes the spins to flip rapidly as a group rather than individually, as is the case for paramagnetism. On a macroscopic level, the behavior of the two is very similar, except at low temperatures when the thermal energy is sufficiently reduced.

If the superparamagnetic particles are placed in an applied field, the energy of the field will cause the spins to align themselves parallel to it, just as with a normal ferromagnet or paramagnet (the degree of alignment depending on the strength of the field and the temperature—as with paramagnets). If the field is taken away, thermal fluctuation causes a ''relaxation'' of the spins, and they begin to flip rapidly between parallel and antiparallel orientations along the easy axis of magnetization (determined by magnetocrystalline or shape anisotropy). This has the effect of causing the material to appear paramagnetic when the magnetization is examined on timescales longer than the flipping frequency (generally $\sim 10^{-9}$ s). The remanent magnetization (which is the magnetization left in the material after removal of the field) decays with time according to the equation:

$$\tau = f_0 \exp\left(\frac{\nu M_s H_c}{2kT}\right)$$

where τ = relaxation time, f_0 = lattice vibration frequency, ν = grain volume, M_s = spontaneous magnetization, H_c = coercivity, k = Boltzmann's constant, and T = temperature.

The relaxation time depends on the height of the energy barrier—which is a function of grain volume and the magnetic properties of the material—and the amount of thermal energy (kT) required to overcome it (Figure 4.6). Using this equation, it is possible to calculate grain volumes above which the magnetization becomes stable or ''blocked'' (i.e., decays over very long periods of time at a given temperature).

4.5 Biological Magnets

For most biological materials, the magnetic permeability is close to that of free space (i.e., diamagnetic), which implies that there is no direct interaction with the magnetic component of electromagnetic fields at low field strengths. However, this is not the case for all biological materials.

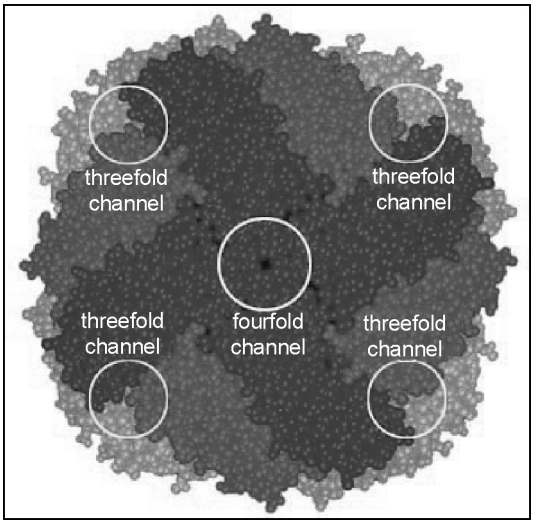

FIGURE 4.7 (See color insert following page 380.) Model of the ferritin protein showing the peptide subunits and iron transport channels. (From www.chemistry.wustl.edu/~edudev/LabTutorials/Ferritin/FerritinTutorial.html. With permission.)

Most magnetic (paramagnetic and ferromagnetic) materials in organisms are compounds of iron—and in particular, iron oxides. Virtually all organisms require iron to function normally. This is mainly due to its redox activity, which allows it to play an important role in energetic biochemical reactions. In organisms, iron is stored as the mineral ferrihydrite ($5Fe_2O_3 \cdot 9H_2O$) within the iron storage protein ferritin. It consists of a 12-nm hollow spherical protein shell made up of 24 subunits (Figure 4.7). The core of ferritin protein is 8 nm in diameter, and it can hold up to 4500 iron atoms in the form of ferrihydrite. Iron is transported into and out of the core through three- and fourfold channels in the shell. During transport, highly toxic Fe(II) is oxidized to Fe(III) for storage as ferrihydrite (Harrison and Arosio, 1996). The specific iron biochemistry of ferritin is complex and is not completely understood (e.g., Yang et al., 1998; Zhao et al., 2001).

Ferrihydrite is a superparamagnetic antiferromagnet at body temperature, and as such, its magnetic properties are potentially important for understanding the environmental consequences of electromagnetic field exposure, including exposure to strong fields within magnetic resonance imaging (MRI) scanners. In fact, the development of pulse sequences for MRI of ferritin is leading to novel ways of assessing iron concentrations in the liver and examining iron associated with neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (Clarke and St. Pierre, 2000; Bartzokis et al., 2004; St. Pierre et al., 2004, 2005). These techniques rely on the magnetic fields generated by ferritin to produce contrast in ferrihydrite-rich tissue in much the same way as synthetic superparamagnetic iron oxide contrast agents do (for a review, see Pankhurst et al., 2003).

In addition to ferrihydrite in ferritin, in 1992 Joseph Kirschvink's group at the California Institute of Technology discovered that biogenic magnetite is produced in the human brain (Kirschvink et al., 1992). Later work demonstrated that this magnetic iron biomineral is present in several organs in the human body, including the heart, liver, and spleen (Schultheiss-Grassi et al., 1997).

Magnetite (Fe_3O_4)—a ferromagnetic iron oxide—is also known as lodestone and is a mineral more commonly associated with sedimentary rocks and volcanics. However, it is also found in many organisms. Probably, the most well-known example is the magnetotactic bacterium. These bacteria use chains of single-domain, biogenic magnetite arranged in chains in order to sense the geomagnetic field and use it for navigation—much like a

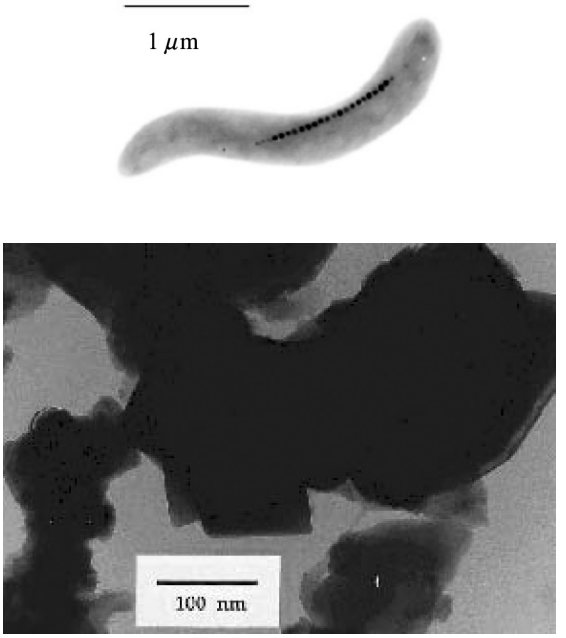

FIGURE 4.8
Transmission electron micrograph of the magnetotactic bacterium MS-1 (top). (From www.calpoly.edu/~rfrankel/mtbphoto.html) Biogenic magnetite extracted from the human hippocampus (bottom). (From Schultheiss-Grassi, PP, R Wessiken, and J Dobson (1999) *Biochim. Biophys. Acta* 1426: 212–216. With permission.)

compass needle (Blakemore, 1975) (Figure 4.8). Although the mechanism by which these organisms produce perfect magnetite crystals is not well understood, it has recently been shown that the process appears to be mediated by specific proteins (Arakaki et al., 2003). Since Blakemore's early discovery, magnetite has been found in a wide variety of animals from bacteria to humans, and in some cases, as with magnetotactic bacteria, it appears to be used for navigation (e.g., Walker and Bitterman, 1989; Walker et al., 1997; Wiltschko and Wiltschko, 2002; for a review, see Kirschvink and Hagadorn, 2000).

Although by 1992, magnetite was known to occur in many organisms, the discovery of biogenic magnetite in the human brain proved controversial. Further work in this area confirmed and extended Krischvink's results, examining not only the occurrence of magnetite in the brain but also its potential role in neurophysiological processes (Dunn et al., 1995; Dobson and Grassi, 1996; Schultheiss-Grassi and Dobson, 1999; Dobson 2001, 2002, 2004; Hautot et al., 2003; Collingwood et al., 2005) (Figure 4.8).

One area of research where the presence of biogenic magnetite in the brain may provide answers to some controversial questions is in the examination of potential mechanisms for the interaction of environmental electromagnetic fields with humans. Two theoretical models have been proposed to demonstrate how biogenic magnetite could act as a transducer of both low-frequency magnetic fields and radio frequency (RF) fields emitted from mobile phones and base stations (Kirschvink, 1992, 1996; Dobson and St. Pierre, 1996). These models rely on the fact that magnetite will couple strongly to the magnetic fields from electrical devices and, either through ferromagnetic resonance effects or through mechanical effects on membrane ion channels, can disrupt the normal functioning of cells in the brain.

Early tests of these models indicate that low-frequency, pulsed magnetic fields from mobile phones may have an influence on cellular activity (including cell death), whereas effects due to ferromagnetic resonance in RF fields are less clear (Cranfield et al., 2003a,b). In addition, magnetite contamination and the presence of biogenic magnetite in model organisms have also been highlighted as potential confounders that could influence the results of studies on the effects of environmental magnetic fields on organisms (Kobayashi and Kirschvink, 1995; Cranfield et al., 2004).

Although magnetite and ferrihydrite are two of the most ubiquitous magnetic materials in organisms, they are not the only ones. Greigite (Fe_7S_8) is a ferrimagnetic iron sulfide found in some iron-reducing bacteria (Posfai et al., 1998). It has a strong magnetic moment similar to magnetite and is thought to be produced as a by-product of iron reduction. Hematite (Fe_2O_3) and wüstite-like (FeO) iron phases also have recently been found within human ferritin (Quintana et al., 2004). And hemosiderin (FeOOH) is a goethite-like iron oxyhydroxide that is antiferromagnetic and is found primarily in pathogenic liver tissue (St. Pierre et al., 1998). In addition to these ferromagnetic materials, other ions and iron compounds, such as hemoglobin, are paramagnetic.

4.6 Magnetic Iron Compounds Related to Pathogenesis

Though iron is an important component of normally functioning organisms, in some cases, it can also be toxic. Because of its redox potential, Fe(II) generally has the potential to do more damage than oxidized Fe(III). For this reason, iron is primarily stored as Fe(III) within ferritin in organisms.

Disruption of the body's normal mechanisms for iron storage can lead to iron overload diseases such as hemochromatosis and β-thalassemia and the deposition of significant amounts of magnetic iron compounds (St. Pierre et al., 1998; Chua-anusorn et al., 2000). These diseases result in the formation of significant iron deposits, predominantly in the liver, which consist mainly of the iron biomineral hemosiderin (FeOOH). Hemosiderin is antiferromagnetic, but can occur as large particles in the body. As with ferrihydrite, both these antiferromagnets contain only Fe(III) and as such have a relatively weak magnetic moment primarily due to lattice defects and, for very fine particles, to frustrated spins on the particle's surface. As mentioned earlier, the presence of these magnetic iron compounds is being exploited for the development of noninvasive MRI monitoring of liver iron in order to track the effectiveness of chelating compounds that are used to treat these diseases (Clarke and St. Pierre, 2000; St. Pierre et al., 2004, 2005). In the brain, disruption of normal iron metabolism results from either disease or trauma and can often lead to pathogenesis (Beard et al., 1993). The accumulation of excess iron is known to induce epileptic activity, primarily as a result of intracranial bleeding due to head trauma. The model of iron-induced epilepsy was first introduced by Willmore et al. (1978), and the electrophysiological responses have been characterized in many studies since then (e.g., Ueda and Willmore, 2000; Engstrom et al., 2001). More recently, evidence shows that iron overload diseases may even predispose a person to epilepsy (Ikeda, 2001).

Although the initial seizure response to trauma and excess iron is relatively swift (Ueda et al., 1998), the long-term consequences of intracranial bleeding on the formation of various magnetic iron compounds in the brain are unclear. Little is known about the formation of iron compounds in the brain of epileptic patients, other than that there appears to be a relationship with an increase in iron (e.g., Willmore et al., 1978; Ueda and

Willmore, 2000; Engstrom et al., 2001). This increase may lead to increased iron loading in the ferritin core or the sequestration of free iron in another form, which could have significant consequences for disease progression. A preliminary correlation between magnetite particle packing geometry and epileptogenic tissue has been demonstrated; however, there is as yet no indication of an increase in magnetite biomineralization associated with temporal lobe epilepsy (Schultheiss-Grassi and Dobson, 1999).

The association of abnormal accumulations of iron with neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's diseases has been known for over 50 y (Goodman, 1953). Although this relationship has been studied extensively, it is not yet clear which iron compounds are present and what their role in these diseases is; however, evidence is mounting that there are likely synergistic mechanisms related to iron and amyloid-β (Aβ, the principal component of Alzheimer's plaques) and other disease-related proteins (e.g., Sayre et al., 2000; Rottkamp et al., 2001; Atamna and Frey, 2004]. Recent work seems to confirm that iron plays a role in disease progression as iron chelators appear to have neuroprotective effects in rat models of Parkinson's disease (Ben Shachar et al., 2004).

Various forms of iron may play a significant role in the biochemical processes that lead to the progression of neurodegenerative diseases. Although there is much speculation on that role, the primary mechanism is thought to be the result of oxidative stress—the generation of free radicals via the Fenton reaction (Connor and Menzies, 1995; Markesbery, 1997; Koppenol, 2001). Recently, Floor (2000) demonstrated the connection between high levels of iron in the basal ganglia and oxidative stress in Parkinson's patients. A disruption of iron metabolism and increased iron in the same region of the brain also has been implicated in Alzheimer's and Huntington's diseases (Bartzokis and Tishler, 2000). Furthermore, iron accumulation has been associated with microgliosis and correlated with increased damage to the CA1 region of the hippocampus via iron–zinc interactions in models of neurodegenerative diseases (Shoham and Youdim, 2000).

It should be noted, however, that some results have shown that the presence of oxidized nucleosides in neurons does not appear to be related to senile plaque material or neurofibrillary tangles in Alzheimer's (Nunomura et al., 1999). In some cases, free radical damage has even been reported to be reduced by Aβ deposition because of the inhibitory role of Aβ-related Zn^{2+} in H_2O_2-mediated toxicity (Cuajungco et al., 2000; Nunomura et al., 2000). More recently, it has been noted that in transgenic mouse models of Alzheimer's, neurogenesis was related to increased deposition of Aβ (Jankowsky et al., 2003). It has been postulated that this may be due to a possible neuroprotective role of Aβ in binding excess redox active iron, which is deposited because of the increased need for iron during neurogenesis (Dobson and Batich, 2004).

Recently, state-of-the-art superconducting quantum interference device (SQUID) magnetometry, nuclear forward scattering, and synchrotron x-ray fluorescence imaging have been employed to evaluate which specific iron compounds are present in these diseases and to map them to structures in the tissue (Hautot et al., 2003; Collingwood et al., 2005; Mikhailova et al., 2005). Early results of these studies indicate that several magnetic iron compounds are associated with these diseases—ferrihydrite (from ferritin), biogenic magnetite, α-iron, and hemosiderin. These results represent a major step toward our understanding of the origin and role of magnetic iron compounds in these diseases.

The role of the various magnetic materials in many organisms, particularly in humans, is only just beginning to be unraveled. After more than two decades of research on magnetic biominerals, it is clear that in many cases they play an important role in biological processes and may provide us with insights into mechanisms of interaction of environmental electromagnetic fields and organisms.

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