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Do naturally occurring magnetic nanoparticles in the human body mediate increased risk of childhood leukaemia with EMF exposure?

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Abstract

Purpose: To develop the hypothesis that magnetic nanoparticles, found in many organisms and often involved in biological reactions to weak electromagnetic fields (EMF), mediate EMF-induced DNA damage which could result in increased risk of childhood leukaemia and other cancers.

Materials and methods: An analysis of current research into magnetic nanoparticles. Physics estimates and the development of the hypothesis that intracellular magnetic nanoparticles chronically change the free radical concentration and can mediate the enhanced rate of DNA damage in hematopoietic stem cells.

Results: The properties of magnetic nanoparticles are considered and the naturally occurring magnetic field generated by a magnetic nanoparticle within a cell is calculated to be in the range of about 1–200 millitesla, which exceeds the level of the natural geomagnetic field by orders of magnitude. Experiments are summarized on the biological effects of static magnetic field in this range. It is shown that magnetic nanoparticles can increase the rate of free radical formation by a few percent, in the course of an idealized radical-pair reaction in a cell. A mechanism is discussed that explains how weak alternating magnetic fields, of the order of 0.4 μT, could cause an increase in the rate of leukaemia via millitesla fields produced around superparamagnetic nanoparticles in hematopoietic stem cells.

Conclusions: The postulated presence of magnetic nanoparticles located in hematopoietic stem cells could constitute a cancer risk factor. Superparamagnetic nanoparticles can possibly mediate increased level of leukaemia caused by background exposure to low-frequency weak EMF.

Keywords: *Magnetic nanoparticle, superparamagnetic particle, leukemia, magnetosome, static magnetic field, hematopoietic stem cell, cancer risk factor, radical pair mechanism, singlet-triplet conversion*

Introduction

A number of studies have demonstrated that magnetic nanoparticles found in living tissues are involved in biological reactions to the Earth's magnetic field, in particular in relation to animal navigation and migrating birds (Johnsen & Lohmann 2005). However, the possible role of magnetic nanoparticles in molecular processes underlying cancer development has not yet been discussed.

It has been repeatedly shown that organisms can biochemically precipitate minerals, including magnetic minerals such as magnetite, maghemite, and greigite, see Quintana et al. (2004) and references therein. The presence of magnetic nanoparticles that form magnetite deposits is well documented in many organisms (Bazylinski & Frankel 2004). Magnetic nanoparticles are also found in the human brain and other human tissues (Grassi-Schultheiss et al. 1997). Recently, efforts were undertaken to identify genes required for biogenic magnetite synthesis and arrangement in bacteria, e.g., Fukuda et al. (2006). Membrane-enclosed crystals of magnetite are often called magnetosomes; in this paper we will use this term as a synonym of 'magnetic nanoparticles' in organisms.

Ferritin, accumulating thousands of iron atoms is necessary for magnetite production from the ferrihydrite it contains, e.g., Liu and Theil (2005). The time-course of the formation of magnetic nanoparticles, magnetite crystals, was analyzed in bacteria by using quantum magnetic measurements (Vali et al. 2004) and cryo-electron tomography (Scheffel et al. 2006). These studies have shown that the formation of 5–10 nm magnetite crystals from ferrihydrite in ferritin cores occurs within 30 min. Larger crystals

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grow during several weeks. The rate of magnetite formation in higher organisms is yet unknown. Unlike in bacteria, nanoscopic magnetic crystals in animals may be a byproduct of biochemical processes utilizing Fe ions (Quintana et al. 2004).

In the presence of hydrogen peroxide or superoxide, ferrous and ferric ions catalyze production of the highly reactive hydroxyl radical in the Fenton/Haber-Weiss reactions. As is shown in (Kruszewski & Iwanenko 2003), the sensitivity of some cells to hydrogen peroxide, the substrate of the Fenton reaction, may be caused by Fe ions, likely to be present in the form of the so-called labile iron pool. It is weakly chelated Fe ions, including those in the cell nucleus, that can quickly interact with numerous iron-containing proteins, like ferritin. Then abnormalities in functioning of proteins regulating the labile iron pool may result in producing magnetite nanoparticles in an appreciable quantity.

The biological role of magnetic nanoparticles in higher organisms is not completely understood (Binhi 2002). The question is whether the consequences of their presence in biological tissues are limited only to magnetic orientation and/or navigation by migrating animals, or can magnetic minerals also take part in destructive processes in cells and in particular mediate the influence of external low-frequency magnetic fields (MF) on such processes?

The density of magnetosomes in the human brain was measured to be more than 5×10^6, and in meninges more than 10^8 crystals per gram of wet weight (Kirschvink et al. 1992). About 90% of the particles measured in this work were 10–70 nm in size, and 10% were 90–200 nm. Subsequent studies have shown that the concentration of magnetite/maghemite in human tissues varies from tens to hundreds ng per gram (Grassi-Schultheiss et al. 1997) and equals about 50 ng/g on average in the human brain (Schultheiss-Grassi & Dobson 1999).

There are some indications that biological cells are not indifferent to magnetic nanoparticles. Experimentally, ultrafine particles 12–14 nm in size were shown to be internalized by human monocyte cells and to significantly increase, by 40–45%, the release of free radicals (Simko et al. 2006). The severity of neurodegenerative diseases has been found to correlate with the amount of magnetite in the human brain, e.g., Bartzokis et al. (1997). A well-known link between excessive iron content in the brain and neurodegenerative diseases is explained in the literature by both direct influence of toxic ferrous ions (Roth et al. 2000) and indirect influence through biogenic magnetite Fe_3O_4 (Hautot et al. 2007). Magnetite-containing small artificial polymeric particles influenced the dynamics of radical pair (RP) reactions in micelles (Scaiano et al. 1997).

Magnetic nanoparticles, independently of their origin – external, through internalization (Weissleder et al. 1990), or endogenous, through the direct crystallization from ferritin-ferrihydrite – can affect RP reactions to promote formation of free radicals. It occurs because magnetic nanoparticles generate their own MF that changes the rate of magnetosensitive RP reactions. As was noted in (Binhi & Chernavskii 2005), MF produced by magnetic nanoparticles around themselves are orders of magnitude greater than the geomagnetic field. Therefore, magnetic nanoparticles can be an important endogenous source of chronic magnetic exposure facilitating free radical formation around the particles. It is important that an external MF, rotating the nanoparticles' magnetic moments and consequently their MF, can thus control the free radical formation.

Magnetosensitive RP reactions are often considered to be a possible primary mechanism of magnetoreception. For example, the evidence for this is rather robust in birds (Wiltschko & Wiltschko 2006). An idealized magnetosensitive chemical reaction may be depicted as

$$\mathrm{M} \leftrightarrow \dot{\mathrm{A}}\,\dot{\mathrm{B}} \rightarrow \dot{\mathrm{A}} + \dot{\mathrm{B}}$$

where M is a molecular precursor, $\dot{\mathrm{A}}$ and $\dot{\mathrm{B}}$ are free radicals, and the intermediate $\dot{\mathrm{A}}\,\dot{\mathrm{B}}$ is a RP in a virtual cage formed by the molecules of the surrounding viscous medium. The spin state of an RP is described by singlet-triplet states: The singlet state with zero total spin, and three triplet states with unity total spin and different components along a selected axis. Generally, in biological reactions, the stable precursor molecule or recombination product M occurs only in zero-spin state. Therefore, as assumed in spin chemistry, the rate of recombination is proportional to the probability of the RP being in a singlet state, e.g., Salikhov et al. (1984). MF affects the evolution of the RP spin state through the magnetic moments of electrons and nuclei. This means that MF causes singlet-triplet transitions, or mixing, and alters the probability of the singlet state. Consequently, the rate of recombination $\mathrm{M} \leftarrow \dot{\mathrm{A}}\,\dot{\mathrm{B}}$ may change depending on the MF value. Thus, MF can also change the rate of free radical formation.

Singlet-triplet (S-T) mixing may proceed mainly through the known Δg mechanism and the hyperfine interaction mechanism, with the characteristic MF values in about the tesla and 0.5–5 millitesla range, respectively. There is also a particular mechanism related to the hyperfine interaction and called 'low-field-effect' (LFE), which originates from the oscillations of the spin state populations in a low field 0.1–1 mT, e.g., Timmel et al. (1998), and the mechanism that results from the RP energy levels crossing in higher fields.

As is shown below, the MF near the nanoparticles discussed attains as much as about 0.2 T and decreases to the geomagnetic field level at the distance of about 0.5 micron. We note also a unique MF nonuniformity around nanoparticles, which makes the basis for an additional mechanism of S-T mixing.

In the above RP reaction, newly-created RP are mostly in the singlet state, so that immediate recombination is a dominating process. However, a small portion of RP generates individual free radicals that escape into solution. For these RP, due to the hyperfine interaction (HFI) mechanism, the probability of recombination increases and that of the free radical formation decreases with growing MF. In contrast, the Δg and LFE mechanisms, as well as the additional mechanism that is effective in a nonuniform MF, facilitate free radical formation as the field grows. On the whole, conditions for these three mechanisms are more lenient than those for the HFI mechanism, because the latter requires not only electron spins but also nuclear spins to be involved in the magnetic interactions. Therefore, summarizing, we assume that high nonuniform magnetic fields promote the formation of free radicals in living tissues as a basic tendency of spin magnetic effects from magnetic nanoparticles. Detailed calculations are given below.

There are physical constraints on RP capable of responding to MF. Certain relations should exist between different characteristic times of the processes involved, among which are: S-T mixing under MF, electron spin relaxations, molecular dynamics of radicals in viscous media, and elementary event of the chemical process. In particular, chemical process should be slow enough to allow appreciable S-T mixing to occur. These constraints significantly reduce kinds of radicals that can form magnetosensitive RP. For example, the hydroxyl radical that lives about a nanosecond in water media could hardly form a pair with another radical. Besides hydroxyl radical, there are also other products of molecular oxygen collectively known as reactive oxygen species; some of them are radicals: Superoxide, hydroperoxyl, and others. Oxygen radicals, highly destructive molecules, are very active chemically. Their chemical lifetimes are relatively short, from units to hundreds of picoseconds. Even if they formed spin-correlated pairs with other paramagnetic molecular intermediates, there would be no time for spin magnetic effects to occur. At the same time, singlet oxygen and so its derivatives may be a byproduct of other RP reactions sensitive to the MF (Liu et al. 2005). Most probable are those formed by organic radicals, which often live about 100 ns and more due to their relatively low mobility and small steric factors.

Thus, on the one hand, various tissues of the human body can contain physiological or contaminating magnetite in the form of both agglomerated and single magnetic nanoparticles. On the other hand, magnetic nanoparticles change the rate of some RP reactions in their vicinity. Which cells could be most sensitive to such an effect? We will show that intracellular magnetic nanoparticles can cause a chronic increase in the free radical concentration and, hence, in the enhanced rate of DNA damage in hematopoietic stem cells (HSC). These cells are thought to be one of the primary places where acquired mutations can accumulate (Huntly & Gilliland 2005). In this paper, it is postulated that some higher organisms may have an abnormally increased content of superparamagnetic (SP) nanoparticles in HSC. The content of the particles is low enough not to be detected by ordinary magnetic methods, for some reasons discussed below. However, it is high enough to appreciably contribute to DNA lesions.

A portion of the free radicals, naturally occurring near DNA due to thermal, photo, or radio activation, appear because of RP reactions that depend on MF. Proteins and DNA can confine radicals long enough for spin MF effects to happen (Mohtat et al. 1998). Therefore, intracellular magnetic nanoparticles need not be in contact with DNA to promote its damage. Such nanoparticles can change the rate of free radical formation remotely, by their own MF extending for hundreds of nanometers. In addition, excessive free radicals cause a higher rate of acquired mutations not only by direct DNA damage but also by breaking the functionality of the proteins involved in the DNA repair system and in the immune system that removes cells with unrepaired genes.

To elaborate the hypothesis that magnetic nanoparticles can contribute to cancer development and that SP nanoparticles can mediate increased risk of childhood leukaemia, we will discuss: (i) The properties of magnetic nanoparticles and the average MF generated by magnetic nanoparticles, (ii) some recent experiments on the biological effects of static MF of the order of those generated by magnetic nanoparticles, (iii) an idealized free radical reaction and an increased rate of free radical formation in a cell, and (iv) a mechanism that explains how background power-frequency MF can cause enhanced leukaemia incidence mediated by SP nanoparticles in HSC.

Results

Magnetic nanoparticles are small magnets that behave like a compass needle. On the one hand, they can rotate in an external MF, thus exerting a pressure on biological tissues. On the other hand, they produce their own relatively large MF. In turn, this MF can affect magnetosensitive biochemical reactions.

Magnetic nanoparticles may be present in an organism by a number of processes: (i) They can penetrate through the organism's surface as natural pollutants, especially as particles of iron oxides that abound in nature; (ii) artificial magnetic nanoparticles may be introduced into an organism with certain aims and penetrate through cell membranes, e.g., Rodriguez et al. (2005); and (iii) magnetic nanoparticles can appear inside biological tissues in the course of natural process of biomineralization.

Magnetosomes have a magnetic moment and as a consequence they produce their own MF. This MF is not small, though it quickly decreases with distance. We will consider the idealized case in which a magnetosome is a sphere of radius ρ with a point magnetic moment $\boldsymbol{\mu}$ in its center. In the point $\mathbf{r} = \mathbf{n}r$, the magnetic moment generates MF $\mathbf{B} = [3\mathbf{n}(\boldsymbol{\mu}\mathbf{n}) - \boldsymbol{\mu}]/r^3$ (CGS units), where $\mathbf{n}$ is a unit vector in the direction of $\mathbf{r}$ and magnetic permeability of the surrounding medium is taken unity.

We will find the MF value averaged over all the orientations of the magnetosome. Unlike studies of orientationally ordered RP in a mechanism of animal navigation (Ritz et al. 2000), it is not necessary here to take into account the particle orientation. From the above expression for $\mathbf{B}$ it may readily be shown that the averaged field B_{av} around the particle surface may be given with 2% accuracy by:

$$B_{\mathrm{av}}(r) = \mu\sqrt{2}/r^3 \qquad (1)$$

for values of r greater than the magnetosome radius ρ. The magnetic moment μ is equal to $v\mathcal{J}$, where $v = 4\pi\rho^3/3$ is the magnetosome volume and $\mathcal{J} = 480$ G ($\mathcal{J} = 4.8 \times 10^5$ A/m in SI units) is the saturation magnetization of magnetite Fe_3O_4. Figure 1 demonstrates the dependence of B_{av} on the distance from the magnetosome surface $r - \rho$. As seen, the average magnetic flux density generated by the nanoparticle varies in the range 1–200 millitesla (mT) at distances up to 100 nm. These values are orders of magnitude

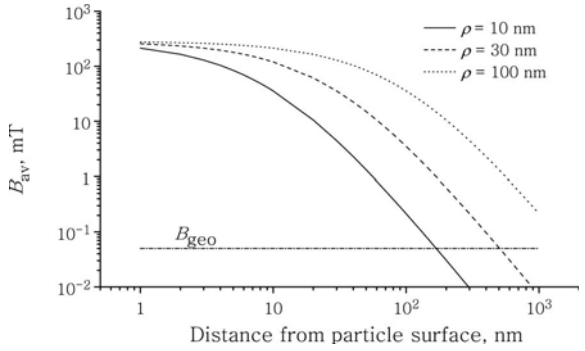

Figure 1. Average MF generated by an idealized magnetosome, at different magnetosome radii. The MF of magnetosomes far exceeds the level of the geomagnetic field.

greater than the geomagnetic field $B_{\mathrm{geo}} \approx 0.05$ mT. The question posed is: Do such fields cause biological effects?

A clear distinction should be made between studies involving static MF and extremely-low-frequency (ELF) MF. Unlike static fields, variable MF induce electric currents in tissues, which may exceed natural biological currents. It occurs when the frequency-amplitude product of an ELF MF is greater than 10 Hz $*$ mT in the order of magnitude. Particularly difficult for interpretation are experiments, in which a biological system is exposed to an intermittent or pulsed MF. Within the short time intervals, when the MF quickly changes, great electric current pulses appear in biological tissues, which undoubtedly cause significant electrophoretic-like effects. Concerning the radical pair mechanism, it is reasonable to separate those effects that have purely magnetic origin. For this, we focus on the experiments where only static MF or ELF MF not exceeding the above frequency-amplitude limit were used as a magnetic exposure.

Many studies, in which biological systems were exposed to the MF of the mT range demonstrated various biological effects (Volpe 2003, Dini & Abbro 2005, Miyakoshi, 2005). In particular, such MF can increase the level of the DNA damages (Ho et al. 1992, Yokus et al. 2005, Saito et al. 2006), deregulate the cell proliferative/apoptotic activity (Fanelli et al. 1999, Robison et al. 2002, Ghibelli et al. 2006), affect immunity (Jandova et al. 2005) and gene expression (Tokalov & Gutzeit 2004; Hirai & Yoneda 2005). Work (Potenza et al. 2004) reports on mutagenicity of MF, tumorigenicity of MF was assumed in (Thun-Battersby et al. 1999), and MF inhibitory activity with regard to apoptosis and tumor suppressor proteins was observed in (Teodori et al. 2005).

It is often argued that these effects might explain the correlation between childhood leukemia incidence and the enhanced background power-frequency MF at places of residence (Santini et al. 2005, Juutilainen et al. 2006). The latter meta-analysis based on 65 studies should have a particular mention. Overall, when ELF MF were given in combination they enhanced the effects of known carcinogenic, mutagenic or other harmful physical or chemical agents with great statistical significance. A minimum percentage of the studies showing the magnetic effect was found in this analysis at fields between 1 and 3 mT. The RP mechanism having the same peculiarity, shown, e.g., in Figure 2, has been suggested to be a good candidate mechanism for explaining this biphasic dependence.

Several studies investigated the dose-response curves in magnetic effects of the mT MF. These studies have shown that biological effects grew with

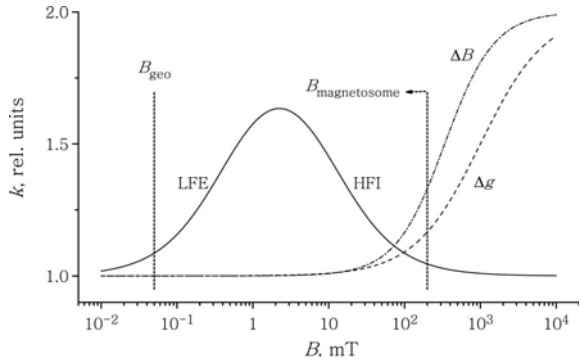

Figure 2. Illustration of relative contributions to the rate of free radical formation from a singlet precursor for different mechanisms of S-T mixing. ΔB contribution is for a particle of radius $\rho = 10$ nm.

the MF magnitude, saturating to about 20–40% at 1 mT or higher MF levels. On the whole, such dependences resemble those for the different modes of the RP mechanism.

Some works reported no effect of static MF on organisms. It is difficult to reconcile the above observations of different biological effects from static MF with known reviews that claim absolute safety of medical magnetic resonance protocols, e.g., Schenck (2005). Medical NMR studies may really be safe due to their relatively short magnetic exposures, despite the strong MF used, on the order of a few tesla. However, this does not rule out the potential health hazard associated with chronic MF exposures and cumulative effects at the level of DNA mutations. Data are often contradictory: some studies report clear mutagenic, co-mutagenic, or toxic effects from tesla-range static MF (Ikehata et al. 1999, Takashima et al. 2004, Miyakoshi 2005), while others do not (Schreiber et al. 2001, Zhang & Zhang 2006). The available epidemiological data are not sufficient to draw any conclusions about potential health effects of static MF exposure (Feychting 2005).

Nonetheless, there are direct experimental indications that RP reactions and free radicals take part in primary interactions of the mT-range MF with biological systems (Rollwitz et al. 2004, Timmel & Henbest 2004, Liu et al. 2005, Yokus et al. 2005). Melatonin, known free radical scavenger, did suppress DNA damage that was induced by a static MF in (Jajte et al. 2001) and by a relatively weak 60-Hz MF (Lai & Singh 2004). Some other free radical scavengers also blocked MF-induced DNA strand breaks (Lai & Singh 2004). The authors proposed that MF initiate an iron-dependent free radical generation process in cells, which can lead to genotoxic changes. (Lupke et al. 2004) found that human umbilical cord blood-derived monocytes released reactive oxygen intermediates under the exposure to 50-Hz MF. High priority is assigned by the World Health Organization to studies of the comutagenic effect of static MF associated with possible changes in the rate of RP reactions (WHO 2006). Thus, many reasons exist for the biological effects of MF in the mT range, which vary roughly as the MF value and saturate in higher fields, to originate from RP reactions.

Magnetosensitive reactions may include also reactions that involve paramagnetic intermediates in higher spin states and those formed by enzyme substrate complexes (Afanasyeva et al. 2007). In this paper, for the sake of simplicity, we will consider only the RP reactions. For a precursor molecule M in a zero-spin state, such a reaction can be represented in the following way

$$\mathrm{M} \underset{p}{\rightleftarrows} (\dot{\mathrm{A}}\dot{\mathrm{B}})^{\mathrm{S}} \rightarrow \dot{\mathrm{A}} + \dot{\mathrm{B}}$$
$$q \nwarrow \searrow \nearrow$$
$$(\dot{\mathrm{A}}\dot{\mathrm{B}})^{\mathrm{T}}$$

where p is the recombination rate constant, q is the rate constant of the magnetically induced S-T mixing. The rate constant of free radical formation, which does not depend on the state of the RP, is taken unity. From this kinetic schema, differential equations can be derived for the concentrations of M, $\dot{\mathrm{A}}\dot{\mathrm{B}}$ in both states, and $\dot{\mathrm{A}}$, $\dot{\mathrm{B}}$. Their solutions are different in the cases of the S-T mixing of different nature.

In a stationary state, within some reasonable idealizations and with an assumption $p \gg 1$ (low free-radical outcome), the relative rate of free radical formation $k \equiv \mathrm{d}[\dot{\mathrm{A}}]/\mathrm{d}t = \mathrm{d}[\dot{\mathrm{B}}]/\mathrm{d}t$ may be derived in the form $k = 1 + 1/(1 + 1/q)$, where the rate constant q explicitly depends on the MF, as in the case of the Δg mechanism. Naturally, the rate k equals unity at $q = 0$ and k equals 2 at large q.

Where the rate constant $q = q_0$ does not depend on MF, just the number of channels of the S-T mixing varies with the MF. It occurs in the case of the hyperfine interaction mechanism and other mechanisms related to the spin energy levels crossing, or changing the levels degeneracy. For the hyperfine interaction mechanism, the number of channels drops from 3 in zero field to 1 in a high MF. Then the relative rate of free radical formation for the case of maximum magnetic effects takes the form $k = 1 - 1/(2 + 1/2q_0)$. Formally, $q_0 = 0$ gives $k = 1$, i.e., that in $B = 0$; and a large q_0 gives $k \approx 1/2$.

Thus, in any case, the rate can increase or decrease in about two times. It is purely chemical kinetic limitations, and all magnetic effects may develop only within these limits.

The above expressions for k show that the contributions of all the mechanisms have the same

motif of a curve with saturation. On the whole, only characteristic MF, at which the saturation occurs, have specific values for different mechanisms of the S-T mixing. The following values $B_{\mathrm{lfe}} = \hbar/\tau\mu_{\mathrm{B}}$, $B_{\mathrm{hfi}} \sim \hbar\, A_{\mathrm{hfi}}/(g\mu_{\mathrm{B}})$, $B_{\mathrm{J}} \sim 2\mathcal{J}_{\mathrm{e}}/\mu_{\mathrm{B}}$, and $B_{\mathrm{g}} \sim \hbar/(\tau\mu_{\mathrm{B}}\Delta g)$ are the characteristic fields related to the LFE mechanism, the hyperfine mechanisms, the mechanism where S-T mixing is associated with the electron exchange interaction, and the Δg mechanism respectively. In these estimates, $\hbar$ is Planck's constant, τ is the RP lifetime, μ_{B} is the electron magnetic moment, $g \approx 2$ and Δg are g-factor and their difference for two radicals, A_{hfi} is the hyperfine interaction constant, and $\mathcal{J}_{\mathrm{e}}$ is the electron exchange energy. For organic radicals, usual values are $\tau \sim 10^{-9}$ s, $\Delta g \sim 10^{-3}$, and $A_{\mathrm{hfi}} \sim 10^{9}$ Hz, so that $B_{\mathrm{hfi}} \sim 10$ mT, and $B_{\mathrm{g}} \sim 1$ T. Low-field effects may develop in MF as small as $B_{\mathrm{lfe}} \sim 0.1$–1 mT. However in so relatively small MF, the spin evolution is slow, and the RP lifetime should be long enough, of the order of $\hbar/\mu_{\mathrm{B}}B_{\mathrm{lfe}} \sim 10^{-7}$ s, for the S-T mixing to occur. The possible quantity of such radical pairs in organisms is unknown today. The exchange mechanism (J-mechanism) will not be discussed here, for it seldom occurs.

It is impossible that all the S-T mixing mechanisms are effective for the same RP, since the conditions of their implementation are different. The case of the two low-field mechanisms coexisting is frequently discussed. Then, taking into account that magnetic effects defined in terms of the relative rates are usually markedly smaller than unity, we may conveniently combine their contributions into a single semi-phenomenological approximate expression

$$k = 1 + \frac{C_{\mathrm{lfe}}}{1+B_{\mathrm{lfe}}/B} + \frac{C_{\mathrm{hfi}}}{1+B_{\mathrm{hfi}}/B} \qquad (2)$$

Here coefficients C are the 'weights' of the contributions of different mechanisms. The curve on Figure 2 illustrates the MF dependence (Equation 2) for the coefficients equal to unity, in magnitude. The decrease in free radical production with increasing MF due to the HFI mechanism is taken into account. Such MF-dependences are typical for long-lived RP (Timmel & Henbest 2004). For comparison, Figure 2 shows a typical contribution of the Δg mechanism and ΔB mechanism that is described below. Also shown are the approximate value of the geomagnetic field B_{geo} and MF near a magnetic nanoparticle. Complex curves associated with three mechanisms coexisting, the hyperfine, exchange, and Δg mechanism, are reported for paramagnetic intermediates within a substrate-enzyme complex in (Afanasyeva et al. 2007).

As is seen in Figure 2, MF generated by a magnetosome covers mainly the area of low-field mechanisms, but also captures partly that of the Δg mechanism. Due to a variety of different radical pairs in organisms and the conditions of their appearance there is no single form of the MF-dependence that would be a general characteristic for the magnetic effects through the RP intermediates. Hence, it is reasonable to separately estimate possible contributions of each of the foregoing mechanisms to the effect of magnetic nanoparticles on the rate of free radical formation.

Since both the own MF of a magnetosome and the rate of production of free radicals around it strongly depend on the distance between the RP and the magnetosome, an estimate of average changes is necessary. In estimating of the average rate of free radical formation we will integrate the expression that represents the relative contribution, i.e., $K \equiv 1/(1 + B_0/B)$, where parameter B_0 is a characteristic MF specific for each kind of the mechanisms.

Averaged value of K over a volume of radius R surrounding a magnetosome of radius ρ is of interest. In calculations, the averaged MF of a magnetosome (Equation 1) is taken for B. Averaged value of K may then be calculated in the form:

$$K_{\mathrm{av}} = \frac{1}{a(R^3/\rho^3 - 1)} \ln \frac{1 + aR^3/\rho^3}{1 + a}, \qquad (3)$$

where dimensionless parameter a satisfies the relation $a \equiv 3B_0/(4\pi\sqrt{2}\mathcal{J})$. The average contribution to the rate of free radical formation (Equation 3) is plotted on Figure 3 as a function of R/ρ at different values of a calculated for the characteristic MF of each of the mechanisms of S-T mixing.

Particular attention should be paid to an additional mechanism of the S-T mixing whereof nature is similar to that of the HFI mechanism. In a sense, this mechanism is close to the phenomenon of spin catalysis, stimulation of radical reactions by changing the spin state of reactants by a third paramagnetic particle (Buchachenko & Berdinsky 2002). This

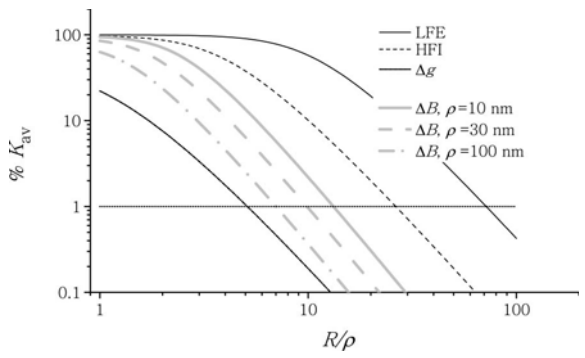

Figure 3. The averaged rates of free radical formation in a volume of radius R surrounding a magnetosome of radius ρ for different mechanisms of S-T mixing.

mechanism exists in highly non-uniform MF; as far as we know, it has not been addressed in the literature. Near a magnetosome, the MF gradient can reach as much as 10^7 that of a usual NMR tomograph and be close to that of the electron spin magnetic moment, at a characteristic distance of about 1 nm. A unique situation is that, unlike a single spin, a magnetosome non-uniform MF covers much greater space.

The difference in spin precession rates of the two electrons of a RP, which results in S-T mixing, may be caused not only by the difference in electron g-factors, but also by the difference ΔB of the local MF at the electrons. Then ΔB rather than the MF is a characteristic parameter. Since the difference in the electron precession rates is now $g\mu_B\Delta B/\hbar$, then the characteristic MF difference equals $\Delta_0 B \sim \hbar/(\tau g\mu_B) \approx 5$ mT. On the other hand, it follows from Equation (1) that the magnitude of ΔB generated by a magnetosome is proportional to B: $\Delta B(r) = 3B(r)\Delta r/r$, where Δr should be a mean distance between the RP electrons, usually 1 nm in the order of value. This enables one to use the same ansatz to evaluate the average value of K, i.e., $K = 1/(1 + \Delta_0 B/\Delta B)$. As a function of B, this dependence, more precisely $k = 1 + K$, is plotted on Figure 2. The result of the averaging gives the following equation, where a tabulated integral is used to avoid a lengthy mathematical expression

$$K_{av} = \frac{3}{b^3(R^3/\rho^3 - 1)} \int_b^{bR/\rho} \frac{x^2}{1 + x^4}\,dx, \quad b = \left(\frac{\rho\Delta_0 B}{4\pi\sqrt{2}\mathcal{J}\Delta r}\right)^{1/4}$$

This dependence is also shown in Figure 3 for different magnetosome radii.

As is seen, within the space limited by about ten-fold magnetosome radius, averaged contributions to the rate of free radical formation may be as large as a few percent as compared to the level corresponding to the absence of magnetosomes. The presence of magnetic nanoparticles in cells results in a *chronic* magnetic exposure. In this case, even a few percent changes in the rate of RP formation might be biologically significant due to accumulation of their contribution to degeneration of DNA. In this sense, particularly effective is the LFE mechanism, since the scope of his impact spreads almost all over the cell volume. At the same time, the LFE mechanism is only possible for long-lived RP. Δg mechanism is effective only at distances less than a few magnetosome radii, which nonetheless may also be of the order of a cell size for large magnetosomes. We note that the hyperfine mechanism lowers the rate k and may be of our interest only for RP born from triplet precursors. The ΔB mechanism is simplest and probably most effective since it requires neither a difference of g-factors, nor the presence of magnetic nuclei in radicals. However, for this ΔB mechanism to work, radicals are not to be quickly shuffled, since otherwise they would experience the same averaged MF.

On the whole, due to a large variety of RP in organisms, it is not possible to predict which type of the foregoing S-T mixing mechanisms will prevail. However, it is clear that magnetic nanoparticles can significantly shift the rate of the reactions with paramagnetic intermediates practically by all known and one additional mechanisms. At that, the rate of free radical formation in cells may be chronically enhanced by a few percent, which is likely to be a risk factor for DNA damage.

Discussion

Many epidemiological studies examined a possible cancer risk of the background electromagnetic fields of power frequency. Some of them revealed a correlation between the rate of childhood leukemia incidence and exposure to power-frequency MF of about 0.3–0.4 μT, while others, in a lesser number, did not; these studies were analyzed, for example, in (Ahlbom et al. 2000, Greenland et al. 2000). The International Agency for Research on Cancer has classified MF as possibly carcinogenic to humans. The nature of the processes underlying this association remains unclear. This paper suggests a magnetosome-related explanation.

It is generally accepted that mutation of genes, whose products control the cell cycle, mediate apoptosis and signal transduction, maintain genomic stability and cellular senescence, is central to carcinogenesis, e.g., Venitt (1996). In this sense, stem cells are especially vulnerable: each cell is a perfect integrator of acquired mutations. In particular, HSC are considered to be the cells where acquired mutations can rapidly accumulate and lead to the increased probability of leukemias (Gilliland et al. 2004).

Besides spontaneous mutations caused by natural reasons, there are external causes of mutations such as various chemicals, aggressive free radicals, radioactive and ultraviolet radiations. A possible source of mutations, not addressed in the literature until now, is magnetic nanoparticles *chronically* exposing nearby molecules to rather strong MF, which in turn can promote formation of free radicals.

Magnetosomes are often assumed to underlie the observable biological effects from exposure to weak magnetic fields (Binhi & Rubin 2007). Recent studies have shown that non-linear stochastic dynamics of a magnetic nanoparticle fixed in the cytoskeleton may be a basis for explaining biological effects from MF of as low as 0.2 μT (Binhi & Chernavskii 2005). Magnetic nanoparticles,

depending on their size and substance, are in a multidomain, single-domain or SP state. Biological formation of multidomain particles is rare, for they are too large. Single-domain magnetite particles are of about 15–100 nm in radius. The magnetic moment of such particles is rigidly bound to their geometry. Consequently, an external MF interacting with magnetic moment exerts a torque on the particle and mechanically rotates it. It was relatively easy to explain how the rotations activate mechanoreceptors, and so single-domain particles have received most attention in bioelectromagnetics.

Unlike single-domain particles, SP particles have their magnetic moments mostly unbound from their geometry. The magnetic moment of an SP particle can be switching between several preferred directions, which are determined by minima of the total magnetic energy. This energy includes the magnetic anisotropy energy of the bulk substance and demagnetizing energy that depends on the particle shape. Under thermal perturbations, the particle chaotically changes its magnetic moment orientation, and so no magnetic moment appears on the average over time. An external MF brings an additional magnetic energy to the particle and makes it to preferably orient in some direction. As a result, the time-averaged magnetic moment appears. However, in a weak MF, it is very small compared to the instantaneous magnetic moment of the particle and it could not explain biological effects of such MF.

In contrast, the average magnitude of the own MF around an SP particle is not a small one and can be orders of magnitude higher than the geomagnetic field. As was shown above, such MF can appreciably change the rate of free radical formation in RP reactions. We note that there is also another possible mechanism of free radical generation by the SP particles. It is associated with the fact that the duration of the SP magnetic switching is relatively short, less than the electron spin-lattice relaxation time in magnetite. The switching process induces eddy electric pulses, in the surrounding cytoplasm, that in turn can break molecular bonds, so creating free radicals.

The ability of SP nanoparticles to quickly switch magnetic moments under thermal perturbations is important. This magnetic switching, a non-inertial process, should be described by the dissipative dynamics with a nonlinear potential function. This approach is quite similar to the stochastic dynamics of single-domain magnetosomes considered in (Binhi & Chernavskii 2005). Different dynamic effects are possible here, including stochastic resonance in an external low-frequency MF and switching rate control by static MF variations at the level of a few tenths of a microtesla. In the case of single-domain magnetosomes, significant (with unit signal-to-noise ratio) effects of such MF are possible for the MF frequencies of not greater than about 0.1–1 Hz, which is the consequence of the rigid bond between the magnetic moment and the particle geometry. Single-domain particles have to mechanically rotate in a viscous media in order to change the direction of their magnetic moments. This rotation is a slow process. There is no such constraint for SP nanoparticles that switch their magnetic moments by quantum jumps. The effective MF frequencies here are much higher, well beyond the power frequencies. Then, external power-frequency MF of the indicated amplitudes could change the dynamics of SP particles significantly.

In this way, weak external power-frequency MF controls switching of the magnetic moment of nanoparticles and makes their relatively strong own MF in a cell to oscillate with the same frequency. A power-frequency component appears in the MF around the particles. At unit signal-to-noise ratio, the intensity of this component is about the same as that of random MF around nanoparticle, i.e., 0.1 T, in the order of magnitude. That is, an alternating weak and uniform external MF induces the non-uniform but strong MF around magnetic nanoparticles. In other words, owing to the nonlinear stochastic dynamics of magnetosomes, the weak external MF reorganizes the local strong MF in time so that its power is redistributing between chaotic and deterministic modes. This periodic strong MF causes free-radicals to appear in a wave-like manner, periodically.

The following different effects specific for these periodic changes in free radical concentration could be considered and numerically estimated, in a model approach:

(i) When the frequency of such periodic changes corresponds to that of the functional activity of some key proteins, their functionality may be particularly vulnerable to the in-phase appearance of the free radicals.
(ii) Due to the non-linearity of many biochemical reactions, they will differently respond to the constant and wave-like excitations, even if the average value of the exciting agent, free radicals here, is the same in both cases.
(iii) Without any damaging effect of free radicals, the periodic strong MF of the particles can unbalance the time-ordered cycles of RP biochemical reactions and the biochemical systems they are involved in and impede adaptation of the cell organelles to the magnetosome MF.

How to test whether SP nanoparticles present a cancer risk factor? The most direct way would be to

observe a difference in the amount of the particles in tissues of cancer patients and healthy people. Another approach is to search for an association between the amount of SP particles and the age at diagnosis of a leukemia. Some indirect indications may come from epidemiological studies. On the one hand, stochastic resonance of magnetosomes in low-frequency MF shows non-trivial static MF dependence of the induced biological effects. On the other hand, an increasing trend of childhood leukemia was associated with certain combinations of household static and power-frequency MF (Bowman et al. 1995). Laboratory studies could also be useful: SP nanoparticles may be artificially introduced into cell cultures or whole animal organisms, which could result in cancer development in chronic experiments.

No data are known so far about possible presence of SP nanoparticles in human blood or marrow, except when they are intentionally introduced into the body as an NMR contrast agent in rather high concentrations.

In HSC, SP nanoparticles were not observed. The following facts markedly impede observation of the particles in stem cells.

(1) The resolution of the X-ray methods of scanning fluorescence microscopy and microprobe absorption near-edge spectrometry is more than about 200 nm, the order of magnitude greater than the average size of SP particles.
(2) The detection limit of advanced X-ray fluorescence microscopes is about 10^{-19} mole per square micrometer of the cross-section of a target, for iron and some other elements. At the same time, a single 12-nm Fe_3O_4 crystal in a 1-micrometer cell gives only 10^{-22} mole of Fe, i.e., orders of magnitude less than the detectable limit.
(3) Not every HSC would necessarily bring an SP particle, even if the entire hematopoietic system was seriously polluted with such particles.

These difficulties make magnetometry a preferred method for possible measuring the SP particle content in HSC. The detection limit of scanning SQUID microscopes at liquid nitrogen temperature, 77 K, is better than about 10^{-10} emu (10^{-13} $A*m^2$). The magnetic moment of a 10-nm Fe_3O_4 particle is about 2×10^{-15} emu. One can readily find, from the Langevin formula, that an ensemble of such particles in a 1 ml sample at the concentration of 10^{-3} ng/ml (less than 10^5 particles) would have the magnetic moment at the detection limit. However, this paramagnetic fraction of the HSC culture sample should be extracted and deposited on a substrate for subsequent low-temperature micromagnetic analysis. Such an extraction presents a complex biochemical/technical task. In addition, possible contribution of SP nanoparticles to the measured quantity can be masked by the SP ferritin (Brem et al. 2006) and trace amounts of the high-spin state heme iron. Therefore, measuring of the SP nanoparticles in HSC requires special methods.

Conclusions

(1) Magnetic nanoparticles present a new interesting object from the viewpoint both of quantum magnetism and of biophysics of cancer.
(2) The magnetic nanoparticles have either natural biogenic origin from intracellular ferritin or appear in cells due to exogenous contamination by widely spread iron oxide nanoparticles.
(3) Magnetic nanoparticles generate their own magnetic field in the millitesla range, which is by orders greater than the geomagnetic field natural for organisms.
(4) The presence of magnetic nanoparticles in human tissues is a source of chronic MF exposure. Such exposure to the mT-range MF changes the rate of reactions with molecular paramagnetic intermediates, particularly the rate of production of free radicals. If a cell contains a magnetic particle, even as small as a few nanometers across, a significant part of the cell is covered by the MF of that particle, so that the average rate of free radical formation may increase by a few percent.
(5) A mechanism of singlet-triplet conversion in spin-correlated radical pairs, specific for magnetic nanoparticles, is considered. It is shown that this mechanism can provide effects comparable with those from the Δg and hyperfine interaction mechanisms.
(6) It is proposed that an increased rate of leukemia in general may originate from magnetic nanoparticles located in hematopoietic stem cells. The enhanced concentration of free radicals in HSC may then result in accumulation of acquired mutations through lesions to DNA and disruption of functioning of DNA repair and the immune system.
(7) A possible causal link between power-frequency background MF exposure and childhood leukaemia may involve isolated SP nanoparticles. Power-frequency MF interacting with the SP particles introduces a temporal order in the formation of free radicals and their damage to DNA and the functions of some cancer-related proteins. A chronic excess in free radical production can impede the development of the immune system and possibly delay its

maturation, thus resulting in an enhanced leukemia incidence in early childhood.

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