4 BIOPHYSICAL MECHANISMS

This chapter considers mechanisms of interaction between radiofrequency (RF) electromagnetic fields (EMFs) and biological systems. Such an approach is necessary in order to fully understand any biological effects that have been observed and to extrapolate effects observed under specific experimental conditions to understand what might occur in other situations. In the absence of an understood biophysical mechanism, the plausibility of any reported biological effects is reduced. The chapter draws principally upon the work contained in international expert group reports from the International Agency for Research on Cancer (IARC, 2013) and the International Commission on Non-Ionizing Radiation Protection (ICNIRP, 2009). A quantitative review of potential mechanisms of interaction between RF fields and biological systems by Sheppard et al. (2008) is also of particular note.

It is well understood that exogenous (externally arising) RF fields can penetrate into the body tissues and deposit the energy they carry as heat (see Chapter 3). Moreover, irrespective of the initial mechanism of interaction involved, all energy deposited in biological tissue is ultimately transformed to heat. Health-related guidelines (ICNIRP, 1998) and standards (IEEE, 2005) have been developed based on heating effects and with the objective of restricting temperature rises in the body to levels where no harm is expected to result.

Biological effects that occur as a result of heating are generally termed *thermal effects*, whereas those that occur through mechanisms other than heating are termed *non-thermal* effects. However, it should be recognised that effects that do not occur as a result of heating could still occur in the presence of significant heating and that this broad categorisation is not always helpful.

As an over-arching principle applying to biophysical interactions, Challis (2005) explains that biological systems (like any other system) are subjected to random fluctuating electric and magnetic fields known as thermal noise. Therefore, in order for a system to respond to an applied RF field, the size of fields induced in the system should be larger than the corresponding random fields.

Sheppard et al. (2008) categorised biophysical mechanisms as either *established* or *proposed*. The established mechanisms relate to plausible biological effects which have been proven to occur through rigorous experiments. On the other hand, the proposed (unproven or not established) mechanisms are those that have not yet gained acceptance through rigorous experiments yielding consistent results, and often have been developed to explain particular experimental observations.

Sheppard et al. (2008) concluded that the dominant established mechanisms are dielectric relaxation[1] and resistive loss which lead to energy deposition and increase of tissue temperature through heating. Pearl chain formation in uniform electric fields (see section 4.4.7), nonlinearity and generation of harmonic frequencies, and demodulation are also amongst established mechanisms operating over all or parts of the RF range. Electron tunnelling and the radical pair mechanism were examples of proposed (unproven) mechanisms. Most other non-thermal mechanisms considered were based upon coupling to specific vibrational modes in molecules, cells or tissues. These mechanisms are not discussed here in detail and would generally be excluded from health-related discussions because, to be biologically effective, they would be accompanied by temperature rises that would overwhelm any other biological response.

4.1 Ionization potential of RF fields

Electromagnetic radiation comprises energy that is carried in quanta known as photons. The energy of each photon is proportional to its frequency, and the total energy carried by the radiation depends on the number of photons and the energy carried by the individual photons. The photon energy, E (in joules), for a radiation of a frequency, f (in hertz), is given by:

$$E = hf$$

[1] Dielectric relaxation relates to the process through which electrical charges that have become displaced on an object such as a cell move back to their equilibrium positions after the externally applied field that caused them to become displaced is removed. This is an exponential process governed by a characteristic of the material known as the relaxation time. The relaxation time is related to frictional forces that slow the movement of charges and it results in a delay in the movement of charges in response to an imposed time-varying field. The frictional forces and delay in the movement of charges lead to energy loss.

where h is Planck's constant, equal to 6.626×10^{-34} Js and equivalent to 4.136×10^{-15} eVs, noting that 1 eV equals 1.602×10^{-19} J.

At radio frequencies the energy of a photon varies from 4.14×10^{-10} eV at 100 kHz to 4.14×10^{-6} eV at a typical telecommunications frequency of 1 GHz and to 1.24×10^{-3} eV at 300 GHz. This is much smaller than the energy required for ionization by ejection or promotion of orbital electrons from atoms of the material through which an electromagnetic wave propagates. The precise threshold energy for ionization depends on the type and state of matter. For example, the minimum photon energies required for removing an electron from biological molecules such as calcium, glucose and water are 6.1, 8.8 and 11.2 eV respectively (Bushberg et al., 2011). Since water constitutes the most abundant molecular target for ionization in living organisms, 11 eV is often taken as the lower limit for ionization in biological systems.

As demonstrated above, a single photon of RF radiation has relatively low energy; therefore, it is not capable of causing ionization. This is why electromagnetic radiation in the RF spectrum is regarded as non-ionizing radiation. Ionizing radiations such as gamma- and X-rays have photon energies above 11 eV and so their damaging effects largely result from ionization taking place in biological cells and tissues. Such effects are not produced by a single photon of RF radiation (Lin, 1978).

In addition to removal of an electron from atoms or molecules, photons can interact with materials by breaking chemical bonds, if they have sufficient energy. The energy required to break various bonds that are found in biological systems has been quantified (Masamichi, 2006). Typical covalent bonds require 1–10 eV, and typical hydrogen bonds require 0.1 eV. Thus, even at a frequency of 300 GHz, the photon energy of RF radiation is still two orders of magnitude too small to break hydrogen bonds, which are the weakest form of chemical bond.

The possibility of adverse effects due to multiple photon absorption at the same site was studied by Prohofsky (2004). In principle, multiple photon processes could shift the incident energy to a region where resonant interactions are known to occur. However, multi-photon absorption requires very intense incident photon beams so the probability is raised that a sufficient number of photons will interact simultaneously with an electron to deliver the amount of energy needed for excitation. Pickard and Moros (2001) demonstrated that this probability is very low, even under an extreme scenario with an SAR of 100 W/kg, which exceeds restrictions in exposure guidelines (ICNIRP, 1998) and is likely to heat the tissue by several degrees.

4.2 Classical interaction mechanism (heating)

As mentioned above, the most recognised and well established mechanism through which biological effects of RF radiation can occur is tissue heating through dielectric and resistive energy losses (Sheppard, Swicord & Balzano, 2008).

The absorption of RF EMF energy by biological systems generates oscillating motions of charged particles and water molecules, which are strongly dipolar and are the major component of biological tissues. Polar molecules move to align themselves with the EMF to minimize their potential energy. Motion and resonant oscillations in polar subgroups of macromolecules (e.g. proteins, DNA) are largely damped by collisions with surrounding water molecules. The damping imposes strict limitations on the energy that can be accumulated in vibrational or rotational modes. If the modes are over-damped (i.e. with decay times less than the time-period of the RF oscillations), resonant absorption does not occur. Damping precludes a direct RF pumping of such modes (Sheppard, Swicord & Balzano, 2008). These collisions disperse the energy of the RF signal into random molecular motion. Tissue heating occurs because the rotational motion of molecular dipoles (including those of water itself) is hindered by the viscosity of water and interactions with other molecules, i.e. the rotational energy is transferred to the surrounding aqueous environment as heat.

In the absence of strong damping by water molecules, compact molecules have their lowest intra-molecular vibrational modes at frequencies no lower than approximately 200 GHz. Acoustic modes[2] can exist in long flexible molecules at arbitrarily low frequencies. However, over-damping by water precludes energy absorption by all modes for frequencies up to the far infrared. Moreover, molecular absorption spectroscopy is usually performed at frequencies above 300 GHz because the spectrum of substances below this frequency usually

[2] *Acoustic modes* occur when adjacent molecules in a lattice move in the same direction as each other during an oscillation whereas *optical modes* occur when adjacent molecules move successively towards and apart from each other during the oscillation.

presents as a continuum without the defined peaks in absorption at certain frequencies that would be characteristic of resonant vibrational motion (Prohofsky, 2004).

The magnitude of motion that results from the interaction of polar substances with electric fields depends on the strength and frequency of the field. In addition, the actual increase in temperature depends on the ability of the organism to thermo-regulate. At higher radiofrequencies, above a few GHz, where the orientation of dipoles cannot keep up with the oscillations of the field, the system behaves like a non-polar substance (Stuchly, 1979).

The energy deposition also depends on the dielectric properties of the cells or tissue, and the local field properties. In principle, it would appear possible to create very high spatial gradients for heat generation within tissue, either because of localised micro-field structure, or because of local enhancements of dielectric property. Nevertheless, even if such conditions were to occur, thermal diffusion in tissue prevents the creation of high spatial gradients in temperature such that localised hot-spots cannot occur on the cellular scale (Liu & Cleary, 1995).

Standards for RF exposure of people are based on protection against adverse effects that might occur due to increases in tissue temperature (head and spinal cord to 38 °C, neck and trunk to 39 °C and limbs to 40 °C). For testes, which are normally at a temperature somewhat below the normal 37 °C core body temperature, the increase in temperature is limited to 1 °C (NRPB, 2004b). An increase in core body temperature of 1°C or less corresponds to a whole body SAR of ~4 W/kg (ICNIRP, 1998). Because RF energy penetration and induced effects are dependent on the frequency of the incident field and the composition of exposed tissues, quantifying SARs in small averaging regions is also relevant for evaluations of localised heating and/or any other effects. For frequencies up to a few GHz, as used in wireless communications, SAR is normally averaged over either 1 or 10 g. Hirata et al. (2008) suggested that the chosen averaging mass should be that which maximises the correlation with local temperature elevation. The dominant factors influencing the correlation between mass-averaged SAR and temperature elevation are the thermal diffusion length in the biological tissue, which largely depends on the blood perfusion rate, and the penetration depth of the RF waves (Hirata, Ito & Fujiwara, 2009).

In a typical exposure scenario where an individual is exposed to RF radiation during the use of a mobile phone against the side of the head, the RF-generated temperature rise in the brain, ranges from 0.05 to 0.12 °C per W/kg (NRPB, 2004a). It is unlikely that any biological effect in the brain would be caused by these small increases in temperature (Repacholi, 2001).

Temperature changes approaching 1 °C are likely to affect several biological processes, although some temperature-sensitive molecular and physiological effects may occur with smaller increase of temperature, i.e. ≤0.1 °C (Foster & Glaser, 2007). Rates of temperature increase can also be important in causing a physiological change. Microwave-induced hearing has been attributed to a rapid rate of heating of head tissue, 1–10 °C/s, which leads to acoustic waves being formed due to expansion of tissue water. This auditory effect is associated with brief pulses (1–10 μs) at frequencies of 1–10 GHz and peak power-densities of ~10^4 W/m^2 and occurs with only small increases in temperature in the head (Foster & Glaser, 2007).

4.3 Induced charge and dipole relaxation

An external RF field can translate and rotate charged and polar molecular structures as well as other cellular components of biological materials. The magnitude of these motions depends on the strength and frequency of the field and may be impeded by inertia and viscous forces. The orientation of polar molecules under the influence of external fields does not occur instantaneously and follows a time-dependent behaviour known as the relaxation process. It also takes some time after the application of an external field for electric charges within the cells and tissue structures to accumulate at the interfaces and reach a new equilibrium state (relaxation). Depending on the size/characteristics of polar molecules, different types of relaxation processes can take place in biological tissues.

In isolation, small charged particles, such as monopolar ions, are able to respond at frequencies up to at least 10^{12} Hz (in the infrared), but the association of ions with water molecules (solvation) means that the dielectric properties of water, with its large dipole moment, are dominant in biological solutions. Water molecules can rotate freely in an oscillating low frequency electric field with little energy loss; however, at frequencies above 10^8 Hz, the rotational inertia of the molecules begins to inhibit rotation, causing energy absorbed from the field to be dissipated by collisions or nearest neighbour interactions in the medium medium (Sheppard, Swicord & Balzano, 2008).

When a dipole distribution is uniform, the positive charges of one dipole cancel the effect of the negative charges from another adjacent dipole. However, when the dipole distribution varies from point to point, a complete cancellation cannot occur. Therefore, an uncancelled charge would be left at an interface surface, which becomes an equivalent bound charge in the material. The relaxation process may therefore be illustrated by considering the response of bound charges to an applied electric field (Lin, 2000; Michaelson & Lin, 1987). In this case, the dynamic force balance equation is given by

$$m\frac{d^2x}{dt^2} = qE - m\omega_s^2 x - m\nu\frac{dx}{dt} \tag{4.1}$$

where E is the applied electric field, x is the displacement of a charged particle in the direction parallel to the field, ω_s is the characteristic frequency of the elastic, spring-mass system, v is the particle collision frequency, and m and q are the mass and charge of the particle, respectively. The force exerted on the particle, mass multiplied by particle acceleration on the left-hand side of equation 4.1, results from an electric driving force qE, an elastic restoring force in proportion to displacement, x, with elastic constant denoted as $m\omega_s^2$, and a retarding damping force proportional to velocity, dx/dt, with damping coefficient, mv.

After Fourier transformation and rearranging terms, equation (4.1) becomes

$$x(\omega) = [(q/m)E]/[\omega_s^2 - \omega^2 + j\omega\nu)] \tag{4.2}$$

where ω is the angular frequency of the applied field and equal to $2\pi f$. Note that the equilibrium position for the charge (x = 0) represents local charge neutrality within the medium. When the charge is displaced from its equilibrium position, a dipole is established between the charge itself and the "hole" that is left behind and bound in the molecular and membrane structure. A dipole moment p is formed by the charge q times the displacement x. For a medium with volume-bound charge density ρ, the total dipole moment per unit volume or polarization P is

$$P = \rho p = [\rho(q^2/m)E]/[\omega_s^2 - \omega^2 + j\omega\nu)] \tag{4.3}$$

The electric flux density D may be expressed in terms of the electric field E and polarization P as

$$D = \varepsilon_0 E + P \tag{4.4}$$

where ε_0 is the vacuum or free space permittivity. For isotropic media, the permittivity may be related to D by the expression $D = \varepsilon E$. These relations together with equation (4.3) give an equation for the permittivity,

$$\varepsilon(\omega) = \varepsilon_0[1 + (\omega_p^2)/(\omega_s^2 - \omega^2 + j\omega\nu)] \tag{4.5}$$

where

$$\omega_p^2 = \rho q^2/m\varepsilon_0 \tag{4.6}$$

Clearly, ε is a complex quantity and can be denoted by

$$\varepsilon = \varepsilon' - j\varepsilon'' \tag{4.7}$$

where ε' and ε'' are the real and imaginary parts of the permittivity and can be obtained by equating the real and imaginary parts of equations (4.5) and (4.7). The relationship between electrical conductivity σ and ε'' is derived from Maxwell's equations and it is

$$\sigma = \omega\varepsilon'' \tag{4.8}$$

The velocity of bound charge motion $v = dx/dt$ can be obtained from equation (4.2), such that

$$\nu(\omega) = [(q/m)E]/[\nu - j(\omega_s^2 - \omega^2)/\omega] \tag{4.9}$$

The finite velocity of charge motion in the material media indicates that the particle cannot respond instantaneously to a suddenly applied electric field. This time-delay phenomenon gives rise to a frequency-dependent behaviour of charge displacement leading to changes in permittivity with frequency or the relaxation mechanism of interaction of electromagnetic radiation with biological systems. It is noteworthy that the same conclusions are reached by performing the inverse Fourier transforms of equations (4.5) and (4.9) and examining the phenomenon in the time domain. Note that the dependence of permittivity on source and characteristic frequencies ω, ω_p and ω_s suggests that the charge displacement and motion given by equations (4.2) and (4.9), respectively, can also be resonant in nature.

Proteins also contain charged groups which are located at sites specific to the atomic arrangements of the molecule. Similarly to isolated ions, these charged groups are bound to water molecules, therefore dielectric properties of biological tissues (at RF) strongly depend on and vary with water content.

4.4 Non-thermal effects (Possible low level interaction mechanisms)

A biophysical mechanism can be specified as non-thermal if the interaction of the RF EMF with living material leads to specific effects other than through heating (Glaser, 2005). Experimentally observed effects are often termed non-thermal when they are not accompanied by a predictable or measurable temperature increase. It is however difficult to ensure that small localized temperature increases, in a cell culture for example, have not occurred during RF exposure.

Non-thermal effects (or effects associated with a negligible increase in temperature) can be defined as biological effects that occur with body temperature changes that are either below 1°C, below what is measurable, or in the range of thermal noise. Several arguments have been presented against the plausibility of a non-thermal mechanism existing by which RF radiation could affect physiological changes. These include:

- Damping effects of the water surrounding biological structures is too strong to allow resonances to exist at radiofrequencies (Adair, 2002);

- The relaxation time – the time for a molecule to return from an excited state to equilibrium – for excitations produced by RF fields (e.g. vibrations in molecules), is similar to the relaxation time for thermal noise, and shorter than the lifetime of the absorption and transfer of energy into resonant modes of oscillating elements in biological systems (Adair, 2003);

- The perturbation of the biological structure induced by the applied field must be greater than the effects of random thermal motion and the effects of other dissipative forces, such as viscous damping by the surrounding medium (Foster, 2000). Random thermal motion of charged components in biological systems (i.e. thermal noise) creates random fluctuating EMFs.

Based on these arguments, Adair (2003) has concluded that it is unlikely that RF radiation with a power density of less than 10 mW/cm^2 (100 W/m^2) could have a significant effect on biological processes by non-thermal mechanisms. Therefore, it is theoretically implausible for physiological effects (except for reactions mediated by free radical pairs) to be induced at exposure intensities that do not cause an increase in tissue temperature (Adair, 2002; 2003; Foster, 2000; Sheppard, Swicord & Balzano, 2008).

Sheppard et al. (2008) have also evaluated several potential mechanisms of interaction of RF radiation with biological systems and concluded that, other than heating and possible effects on reactions mediated by free radical pairs, RF field strengths in excess of system noise (collisions among various molecular oscillators generated largely by thermal agitation) could not alter physiological activities without also causing detectable tissue heating. For example, in order for RF electric fields to induce small changes in protein structure that would affect binding of substrates or ligands to enzymes or receptor proteins, extremely high field strengths would be required (~10^9 V/m). Sheppard et al. (2008) have addressed mechanistic considerations of interactions as explained in the following sections.

4.4.1 Endogenous electric fields

Endogenous (internally arising) electric fields include quasi-static fields that guide and orientate cells during processes such as embryonic development and wound healing. Other physiological processes give rise to fields that have varying amplitude and phase in response to ever-changing physiological surroundings (Sheppard, Swicord & Balzano, 2008). Fields generated by muscles (including the heart) and the nervous system (including

the brain) are summations of discrete electrical pulses from a large number of electrically active cells; therefore they are not harmonically pure. Their spectrum is continuous and generally confined to certain frequency regions up to a few hundred Hz.

Endogenous quasi-static fields have strengths in the range 1–200 V/m (Nuccitelli, 1992), while time-varying fields associated with the central, peripheral and autonomic nervous systems are smaller. For example, Hart and Gandhi (1998) found fields associated with cardiac processes to be a few tenths of a volt per meter in the heart tissues and a few millivolts per meter a distance away from the heart. At cellular membrane level and at sufficiently low frequencies, since the membranes have high resistivity and capacitance (nearly constant for all mammalian cells and equal to 1 F/cm^2), high fields can be produced at the two faces of the membrane. Fields inside the cell are small, as long as the frequency of the applied external field is below the membrane relaxation frequency, which in turn depends on the total membrane resistance and capacitance (WHO, 2007). Gabriel et al. (1996) indicate that the membrane relaxation frequency is typically in the hundreds of kilohertz region.

Any exogenous (externally arising) electric field must be of the same order as the endogenous fields (or stronger) to affect normal physiological functions or any functions associated with them (Adair, 2003; Sheppard, Swicord & Balzano, 2008). Therefore, applied fields much smaller than naturally occurring fields in the same frequency band, can only produce a small perturbation in an on-going process.

Nuccitelli (2003) suggested that a field of 0.1 V/m would not affect a biological system. However, active neuronal circuits studied in vitro in brain slices, respond to extremely low frequency (ELF) electric fields at about this level; while effects on individual neurons required much greater field strength. Furthermore, no mechanisms for inducing changes in cell membrane potential at frequencies above ~10 MHz have been demonstrated.

Applying short pulses (~100 μs) of strong electric fields (e.g. 10–100 kV/m) to cell membranes in order to induce transient pores is called electroporation and allows uptake of drugs, DNA, or other membrane-impermeable substances (Foster, 2000; Sheppard, Swicord & Balzano, 2008). These changes occur without causing significant tissue heating and any consequent thermal damage.

Endogenous fields have different characteristics at low and high frequencies. The low frequency power density of these signals in humans is dominated by electric fields from the heart, leading to a maximum of 0.4–0.6 V/m in the torso and 15 mV/m in the brain. The spectrum of living tissue in the megahertz region and above has the characteristics of a black body at ~ 300 K (see Chapter 2) and shows no sharp peaks in emission or absorption (Sheppard, Swicord & Balzano, 2008).

4.4.2 Specialized sensory systems

Living organisms have electromagnetic field sensing systems that detect heat and light. The signal detecting structures and signal processing by the nervous system utilises environmental signals as stimuli necessary for survival (Adair, Astumian & Weaver, 1998; Torre et al., 1995). Some species detect quasi-static and low frequency electric fields for use in orientation, navigation and defence defence (Sheppard, Swicord & Balzano, 2008).

While specific sensory systems have been shown to exist for low-frequency, infrared and visible radiation, there is no evidence of comparable RF-sensitive receptors in biological systems. Sheppard et al. (2008) argue that the reason for this is that the RF spectrum lacks natural significant coherent sources and was essentially featureless until the advent of modern man-made sources of RF EMF. In other words, the biological systems did not develop ways to detect RF because this would not have given them any survival advantages.

4.4.3 Effects of weak RF fields

Weak RF fields that do not cause heating would be likely to require frequency-dependent resonant absorption or multiple-photon absorption to induce an amplified signal strong enough to overcome intrinsic molecular thermal noise (Sheppard, Swicord & Balzano, 2008). This is because the photon energy of RF radiation is much smaller than molecular thermal energy at body temperature.

Also, biological systems appear to absorb RF signals like a broadband receiver rather than eliciting line spectra characteristic of resonant vibrational motion (Prohofsky, 2004; Sheppard, Swicord & Balzano, 2008). In addition, RF electric field strengths of up to 200 V/m cannot transfer sufficient energy to biological molecules to

alter biological activities or affect thermal noise (kT) fluctuations, such as the opening of voltage-gated ion channels, spatial arrangements of membrane-associated ions, collision rates of charged ligands with proteins, or enzyme reaction kinetics (Adair, 2002; 2003; Sheppard, Swicord & Balzano, 2008).

Adair (2002) suggested that, while coupling of RF EMF to biological systems may exhibit resonance behaviour, strong damping of the vibrational motion by interactions with the aqueous environment prevents the absorption of sufficient energy to induce a biological effect. To significantly affect a biological system, the response from the RF signal must be comparable to or greater than the effect of thermal noise (Adair, 2003).

A biophysical theory of how low-intensity RF-EMF exposures might affect physiological functions involves the alteration of ligand binding to hydrophobic sites in receptor proteins (Chiabrera et al., 2000). Collisions of the ligand ion in the hydrophobic region of the receptor protein would result in loss of its vibrational energy. In order for RF exposures to affect the binding probability of an ion ligand with a membrane protein receptor, basal metabolic energy would have to amplify the effect of the RF field by maintaining the cell in thermodynamic non-equilibrium. Otherwise, the low-intensity exposure would be negligible compared with thermal noise. Other elements of the model that was used to evaluate the effects of low-intensity RF exposures on ligand binding are the extremely fast ("instantaneous") rearrangement of atoms in the hydrophobic core of protein by the ligand ion, the fact that the endogenous field at the protein boundaries is large enough to exclude water molecules from the hydrophobic core, and that the ion-collision frequency near the hydrophobic binding site is much less than it is in water. Chiabrera et al. (2000) recognised that thermal noise must be taken into account when evaluating potential biological effects of RF exposures.

4.4.4 Effects of EMF on specific sites

RF EMF may be directed to specific sites of a biological structure, leading to local areas of enhanced field strength. However, the smallest focal spot of concentrated energy would have a radius of the order of a wavelength, which is much larger than most cells (e.g. at 300 GHz, λ = 1 mm). Thus, on a cellular basis, RF-energy absorption is very small.

Fröhlich (1968) has suggested that incident RF energy may be captured by a large group of oscillating dipoles and integrated into a single mode of coherent vibrational energy. For this to occur and produce a coherent response, Sheppard et al. (2008) suggested that the energy stored in the coupled oscillators would need to be comparable to thermal energy and protected from damping by water or other molecules. In addition, energy and thermal diffusion prevent the formation of significant temperature differences at the cellular and subcellular levels.

4.4.5 Non-equilibrium and non-linearity

Since living systems are not in thermal equilibrium, mechanistic theories on interactions between RF EMF and biological tissues must consider the non-equilibrium and nonlinearity of these systems. In principle, non-linear processes such as rectification can transduce RF signals modulated at low frequency into the frequency range where physiological systems operate (Sheppard, Swicord & Balzano, 2008). The theories on the potential effects on biological systems of RF energy at low field strengths must account for the facts that biological systems do not exist at equilibrium, that the dynamic nature of these systems is controlled by enzyme-mediated reactions, and that primary effects may be amplified by nonlinear biological processes (Georgiou, 2010).

Binhi and Rubin (2007) suggested that biochemical effects may be induced by weak EMFs in targeted systems that are in non-equilibrium states in which the time to transition from an intermediate metastable state to a final active or inactive state may be less than the thermalization time of the induced field.

Prohofsky (2004) has suggested that protein conformation might be affected by RF radiation if amplitudes of specific vibrational modes are altered. However, only intermolecular vibrational modes of proteins and the surrounding tissue occur at radio frequencies and intra-molecular resonant vibrational modes only exist above several hundred GHz. Prohofsky (2004) concluded that the biological effects of RF radiation on macromolecules (proteins and DNA) can only be due to temperature changes because the absorbed energy associated with inter-molecular vibrations is too rapidly converted to heat; i.e. coupling of RF EMFs to the surrounding water (damping) occurs before the energy can be transferred to intra-molecular resonant modes. However, a non-thermal effect might still exist if there were a very strong energy coupling between the inter-molecular and intra-molecular modes and if the effect of water can be isolated. Thus, exceptions to the above-mentioned considerations occur for proteins such as myoglobin or haemoglobin, in which the haem group can oscillate in the protein pocket at lower frequencies. A frequency of 184 GHz is the lowest mode in myoglobin.

4.4.6 Demodulation

Nonlinearity of certain materials can lead to generation of harmonic frequencies and demodulation of signals (Sheppard, Swicord & Balzano, 2008). The possibility that biological tissue can demodulate an RF signal through the non-linear conversion of RF energy and thereby generating a signal within the tissue at the modulation frequency has been studied (Foster & Repacholi, 2004). Generally, RF signals are modulated at low frequencies to which neurons and neuronal networks such as those in the central nervous system (CNS) are particularly sensitive, and so even weak demodulation could be biologically significant. Ionic conduction through membrane ion channels results in demodulation but only at radio frequencies below about 10–20 MHz (Pickard & Barsoum, 1981; Pickard & Moros, 2001).

Challis (2005) suggested that demodulation of higher frequency pulsed RF signals (e.g. 900/1800 MHz GSM mobile phone signals pulsed at 217 Hz) might produce low-frequency electric fields in tissues. This would require there to be a nonlinear response in the biological sample. Except for the case of an incident flux of RF energy in the form of extremely high field strength pulses that causes mechanical vibrations, most oscillators in a biological system respond linearly to the incident low energy photons in the RF spectrum. The dispersion of RF energy into random molecular motion energy occurs without generating harmonics of the incident signal in the energy spectrum of re-radiated photons by the exposed material.

Balzano and Sheppard (2003) considered the possibility that demodulation of high-frequency incident RF signals might arise from nonlinear interactions with biochemically induced transient oscillators in living tissues e.g. the uncoupled electrons of free radicals. If this were to occur, then the spectrum of RF emission energy emitted from the exposed tissue would be altered, producing a second harmonic that would show up as a spectral line at twice the frequency of the incident signal.

Sensitive instruments have been developed to detect the presence of frequency-doubling signals produced by nonlinear interactions between amplitude-modulated RF signals and molecular oscillators vibrating in unison in living cells. These are based on exposing biological samples in cavities designed to be resonant both at the fundamental frequency of an imposed signal and its second harmonic (Balzano, 2003)

Balzano et al. (2008) constructed a doubly resonant cylindrical microwave cavity and showed that it was able to detect frequency doubling arising from the nonlinearity of an exposed microscopic Schottky diode test structure. Cells with a diode-like nonlinearity could demodulate a modulated RF carrier wave and generate low frequency signals in an exposed biological preparation. However, the results showed that demodulated field strengths are usually very weak. Specifically, the ELF electric field detected by a nonlinear material from an incident ELF amplitude-modulated RF electric field of 100 V/m would be no more than approximately 3×10^{-3} V/m in the ELF band (Balzano et al., 2008). Therefore, the voltage developed across a membrane with a thickness of 10^{-8} m can be expected to be more than 3×10^{-11} V which is approximately 10^{7} times smaller than the low frequency membrane voltage noise that limits physiologically significant events in excitable cells (Billimoria et al., 2006; Jacobson et al., 2005; Kole, Hallermann & Stuart, 2006). In summary, the demodulated ELF signal that may exist across the membrane would be irretrievably lost in membrane noise (Sheppard, Swicord & Balzano, 2008).

Kowalczuk et al. (2010) used such a doubly resonant cavity to expose more than ten different types of cellular and tissue samples (normal and cancerous) to continuous wave fields at around ~880–890 MHz. The input powers were 0.1 or 1 mW, and SAR values were approximately 11 W/kg for cells and 2.5 W/kg for tissues at the higher of these powers. The authors found no evidence of nonlinear energy conversion to twice the frequency of the incident signal.

4.4.7 Enhanced attraction between cells for pearl-chain formation

The pearl-chain effect occurs when molecules and cells move under the influence of RF electric fields and rearrange to form chains along the direction of the field (Schwan, 1982; Sher, Kresch & Schwan, 1970; Takashima & Schwan, 1985). The effect has been observed with RF fields of about 125 V/m and at frequencies up to about 100 MHz..

Pearl-chains have been formed with biological materials such as erythrocytes or bacterial suspensions. Under the influence of RF electric fields, electrical charges tend to accumulate on opposite cell surfaces to form induced dipoles, whose orientation changes with oscillations of the field. A dipole–dipole attraction occurs in the process. The attractive forces between the dipoles are enhanced when the cells are in close proximity to each other.

The dipoles then align in the direction of the applied electric field and form chains of many cells or molecules. These chains are mostly single-stranded, although it is possible to form multi-stranded chains.

At frequencies up to about 100 MHz, the precise threshold electric field strength needed to produce the pearl-chain effect depends on frequency, cell or particle size, and pulsing parameters of the applied field. At higher frequencies, the induced dipoles have insufficient time to follow the oscillating field to change their directions.

Both pulsed (single or multiple pulses) and continuous wave (CW) fields are known to produce the pearl-chain effect, with a time constant that appears to be proportional to $1/E^2$, where E is the field strength. A minimum amount of energy proportional to τE^2, where τ and E are the minimum pulse width and threshold field strength respectively, is required to overcome the Brownian forces associated with random motion. The minimum average field strength required for pulsed fields to produce pearl chains is equal to the minimum average field strength for CW fields, suggesting that pulsed fields are no more effective than CW fields in inducing the pearl-chain effect. On the basis that the pearl-chain effect can be produced by a single pulse without a significant temperature rise, the pearl-chain effect is regarded as being caused by forces induced by RF electric fields, not by a biologically significant temperature elevation.

While these effects have been observed using in vitro preparations of cell suspensions, they seem unlikely to occur in living systems. In principle, blood could be regarded as such a cellular suspension, but its motion is in irregular directions in organs and unlikely to become aligned with the field over appreciable volumes, except perhaps in long straight vessels.

4.4.8 Magnetite

Magnetite (Fe_3O_4), found in magnetosomes that are present in the human body, including brain tissue, is a strong absorber of RF radiation between 500 MHz and 10 GHz (Kirschvink, 1996). Low-frequency magnetic fields might also produce biological effects if they induce ferromagnetic resonance in tissues that contain high concentrations of magnetite (Challis, 2005). However, magnetite's concentration is very low (5–100 ppb) in human tissues and the resultant heating should be biologically unimportant at localized SARs below guideline levels (Adair, 1996; Kirschvink, 1996; Pickard & Moros, 2001).

4.4.9 Electron tunnelling

Electron tunnelling, the transfer of electrons through biochemical pathways, is a vital element of energy transduction pathways in living cells (Winkler et al., 1999). The electron donor and acceptor are usually weakly coupled in biological systems (Balabin & Onuchic, 2000). Electron tunnelling between donor and acceptor sites in proteins can proceed via a few or multiple transfer pathways. Electron transfer rates are high when the pathways are simple or there is constructive interference amongst multiple paths. However, the rates are significantly lower for destructively interfering pathways (Sheppard, Swicord & Balzano, 2008). Electron tunnelling in proteins is also relatively slow at very long molecular distances (Winkler et al., 1999).

Electron tunnelling may occur for a group of similar tunnelling pathways that constitute a tube. Tunnelling via tubes can be strongly influenced by changes in the spatial relationship of donor and acceptor sites according to protein conformation and nuclear dynamics. However, none of these are perturbed by the low photon energy of RF signals (Sheppard, Swicord & Balzano, 2008).

If the RF energy absorption is intense, electron tunnelling can be influenced by a temperature increase within complex molecular structures, e.g., proteins. The tunnelling rates are increased by atomic and molecular agitation, opening tubes with constructively interfering pathways or relieving the destructive interference in other tubes. However, very high levels of SAR (>100 W/kg) are required to affect protein conformation (Webb, 1980; Bohr and Bohr, 2000) (Bohr & Bohr, 2000a; b; Webb, 1980).

4.4.10 Radical pair mechanism

Free radicals, which are highly reactive and short-lived molecules or ions with unpaired electrons, are formed when radical pairs dissociate. Scission of a covalent bond in a biological molecule results in the formation of a radical pair, usually as an intermediate stage in some metabolic reaction. If the radical pair lives long enough, a magnetic field can affect the probability of radical recombination and thereby change the reaction yield.

Low-intensity magnetic fields may increase the concentration of free radicals by altering the recombination of short-lived radical pairs with antiparallel spins (Challis, 2005; Georgiou, 2010). The expected increase in radical concentration is 30% or less (Timmel et al., 1998). The extent to which this increase can produce oxidative stress-induced tissue damage (e.g. membrane-lipid peroxidation or DNA damage) is not known. Radicals are involved in intracellular signal transduction as part of normal cellular physiology (Finkel, 2003). Therefore, even small effects on radical concentration could potentially affect multiple biological functions.

To affect DNA recombination and thus the repair of damage caused by radicals, external magnetic fields must act over the times that the radical pairs dissociate ($>10^{-9}$ s). Based on this, Adair (2003) concludes that the effect of RF fields on free-radical concentrations would likely be limited to frequencies of about 10 MHz or less.

Ritz et al (2009) identified a radical pair with a long life time involved in the birds' magnetic compass. The authors studied the effect of external magnetic fields at several frequencies ranging from 0.01 MHz to 7 MHz, with an intensity of 470–480 nT, on robins' behaviour and demonstrated that fields of around 0.6 MHz and above caused them to be disoriented consistently. They concluded that an intense resonance at a Larmor frequency of 1.315 MHz (with a 46 μT static geomagnetic field) is expected for a radical pair in which a radical has a magnetically isolated spin. The strong resonance at a frequency proportional to the intensity of the static field appears to arise from the interaction of the unpaired electron with the external magnetic field to produce a unique energy-level splitting (Zeeman interaction).

Georgiou (2010) reported some studies that provide evidence for the induction of oxidative stress via the free-radical pair mechanism in biological systems exposed to RF radiation. Some of the reported effects include increased production of reactive oxygen species, enhancement of oxidative stress-related metabolic processes, an increase in DNA single-strand breaks, increased lipid peroxidation, and alterations in the activities of enzymes associated with antioxidative defence. Many of the changes observed in RF-exposed cells were prevented by (pre)treatment with antioxidants.

Sheppard et al. (2008) noted that despite the great number of biochemical reactions involving free radicals, there are many restrictive conditions that would make the effect of RF magnetic fields very unlikely in most systems. These include the frequency constraints based on hyperfine coupling strength, radical pair interactions restricted by the necessity for creation of spin-correlated radical pairs that remain in close proximity, radical lifetimes long enough to be affected by an oscillatory magnetic field, relaxation processes slow enough to allow adequate radical lifetime, and static magnetic fields of appropriate field strength.

4.4.11 Biochemical studies

Biochemical studies are usually carried out on cell-free systems such as proteins, membranes and liposomes in order to acquire information on the validity of hypotheses made at the physical or biophysical level and about the way RF exposure might trigger biological effects, possibly leading to health effects.

4.4.11.1 Biological macromolecules

Some studies have addressed the effects of RF exposure on the structure and function of biological macromolecules such as proteins or DNA. These studies aim to investigate whether absorption of RF energy by macromolecules could modify their structure and/or perhaps their behaviour (Fröhlich, 1968).

Bohr and Bohr (2000a) performed a series of experiments on globular proteins, particularly β-lactoglobulin. They exposed protein solutions to RF signals for 5 s in a microwave oven at 2.45 GHz and 800 W, causing a ~0.3°C temperature increase. Using optical rotational dispersion, the authors showed that exposure accelerated conformational changes of the protein. In a second paper Bohr and Bohr (2000b) reported an enhancement of folding and denaturation of the proteins. These observations were interpreted as evidence of coherent RF excitation of vibrational or torsional modes leading to altered conformation of the protein molecules. However, these results did not consider the difficulty of direct excitation of vibrational modes by RF nor the effects of damping (Adair, 2002; Challis, 2005).

Some studies have compared the effect of RF exposure on activity of a thermophilic β-galactosidase with that of conventional heating (Bismuto et al., 2003; La Cara et al., 1999; Mancinelli et al., 2004) and failed to report any changes on structural organization of myoglobin molecule, its internal dynamics and CO (carbon monoxide) binding affinity. The small-amplitude effects of protein misfolding observed by Mancinelli et al.

(2004) are prone to artefacts caused by small variations in the temperature control of the samples and these results are yet to be confirmed (ICNIRP, 2009).

Specific effects on a solution of green fluorescent protein exposed at 8.5 GHz were reported by Copty et al. (2006). Samples were either exposed to RF or heated using resistive heating with maximum RF power corresponding to a calculated SAR of 4 kW/kg and ΔT of 3°C. In both cases, heating produced a decrease in the protein fluorescence intensity and the spectrum became red shifted. For a similar temperature rise, the alteration of fluorescence was larger in the RF-exposed samples, which was interpreted as evidence of a specific non-thermal effect of RF exposure. However, the theoretical and experimental determination of ΔT under RF exposure is very uncertain for any conclusion regarding non-thermal effects (ICNIRP, 2009).

There have been some studies on isolated DNA in solution, reporting a frequency-specific absorption in DNA from plasmids or DNA breakage due to RF exposure in solution (Edwards et al., 1984; 1985; Sagripanti & Swicord, 1986; Swicord & Davis, 1982). However, follow-up studies failed to confirm the early results (Foster, Epstein & Gealt, 1987; Gabriel et al., 1987). DNA breakage was most likely to have been the result of free radical formation due to the use of copper electrodes and hence the presence of copper ions in solution, but not the result of a direct action of RF absorption (Sagripanti, Swicord & Davis, 1987). Further theoretical calculations by Foster and Baish (2000), Adair (2002) and Prohofsky (2004) support the view that viscous damping would be sufficient to make any 'resonant' behavior of DNA molecules in solution very unlikely.

4.4.11.2 Liposomes and membranes

Liposomes are artificial phospholipid vesicles, constructed in the laboratory, which have often been used as models for studies of membrane properties. Early work by Liburdy and Magin (1985) reported an enhanced release of drugs trapped in the liposomes under exposure at 2.45 GHz with an SAR of 60 W/kg. The effect occurred at temperatures below the membrane phase transition temperature of 41°C.

Ramundo-Orlando et al. (2004) exposed liposomes entrapping glycoenzyme ascorbate oxidase to 2.45 GHz, and SAR levels of up to 5.6 W/kg. Exposure at the maximum SAR level reduced enzyme activity, although the conformation of the enzyme was not affected. The authors suggested that RF interactions with the oligosaccharide chains of the enzyme were critical in eliciting this effect. Further work by the same group at 130 GHz using the carbonic anhydrase enzyme led to increased liposome permeability under pulsed exposure, but only when modulation was at 7 Hz and not 5 or 10 Hz (Ramundo-Orlando et al., 2007).

4.5 Summary

A review of established and proposed mechanisms reported in literature suggests that the most important mechanism of interaction between RF and biological systems is the heating of tissues by dielectric and resistive loss.

Other mechanisms have been hypothetically proposed to understand experimental observations that could not be explained by thermal mechanisms. However, as Sheppard et al. (2008) demonstrated, detailed analysis of proposed molecular mechanisms showed that over-damping by water imposes strict limitations on vibrational or rotational modes and precludes a direct RF pumping of such modes.

Some of the proposed mechanisms involve energy levels that are much smaller than the thermal background and, even considering various circumstances for amplification, could not overcome the influence of thermal noise (Sheppard, Swicord & Balzano, 2008). Those mechanisms governed by quantum mechanics are coupled to the thermal noise and subject to the same limitation. Therefore, Sheppard et al. (2008) concluded that there is no mechanistic path whereby RF energy can be directly imparted to selected oscillatory modes of the biomolecular system.

Some proposed mechanisms involve the existence of nonlinear processes in which some of the energy in an RF signal is transferred into lower frequency bands where there are metabolic oscillations, leading to interference with those oscillations. Demodulation of amplitude modulated, including pulsed signals is possible below a radio frequency of about 10 MHz so non-thermal effects could then in principle occur at a lower modulation frequency. However, even without considering demodulation efficiency, the maximum theoretical power that can be demodulated is extremely small (Sheppard, Swicord & Balzano, 2008).

RF energy below thermal levels can affect radical pair-dependent chemistry with possible biological consequences. This phenomenon reflects the quantum mechanical nature of energy level splitting via the hyperfine interaction for certain nuclei of a radical pair. However, magnetic resonance in the gigahertz regime requires a nucleus with an exceptionally large hyperfine coupling constant, indicating that effects on free radical reaction rates are unlikely to be a general feature of biochemistry (Sheppard, Swicord & Balzano, 2008).

Overall, the search for non-thermal effects of RF on biological macromolecules such as proteins and DNA has not generated good evidence to suggest that such effects occur. Overall, there is limited evidence to date that non-thermal RF effects occur in model liposomes although the biological significance of such effects is not clear.

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