Prostaglandins, Leukotrienes and Essential Fatty Acids ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at SciVerse ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Review

A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution

Michael A. Crawford [a,*], C. Leigh Broadhurst [b], Martin Guest [c], Atulya Nagar [c], Yiqun Wang [d], Kebreab Ghebremeskel [d], Walter F. Schmidt [b]

[a] Imperial College, Department of Cancer and Surgery, Division of Reproductive Physiology, Obstetrics and Gynaecology, Room 334, Chelsea and Westminster Hospital Campus, 369 Fulham Road, London SW10 9NH, UK
[b] United States Department of Agriculture Agricultural Research Service, Beltsville, MD, USA
[c] Department of Mathematics and Computer Science, Liverpool Hope University, UK
[d] London Metropolitan University, Holloway Campus, London, UK

A B S T R A C T

Six hundred million years ago, the fossil record displays the sudden appearance of intracellular detail and the 32 phyla. The "Cambrian Explosion" marks the onset of dominant aerobic life. Fossil intracellular structures are so similar to extant organisms that they were likely made with similar membrane lipids and proteins, which together provided for organisation and specialisation. While amino acids could be synthesised over 4 billion years ago, only oxidative metabolism allows for the synthesis of highly unsaturated fatty acids, thus producing novel lipid molecular species for specialised cell membranes.

Docosahexaenoic acid (DHA) provided the core for the development of the photoreceptor, and conversion of photons into electricity stimulated the evolution of the nervous system and brain. Since then, DHA has been conserved as the principle acyl component of photoreceptor synaptic and neuronal signalling membranes in the cephalopods, fish, amphibian, reptiles, birds, mammals and humans. This extreme conservation in electrical signalling membranes despite great genomic change suggests it was DHA dictating to DNA rather than the generally accepted other way around.

We offer a theoretical explanation based on the quantum mechanical properties of DHA for such extreme conservation. The unique molecular structure of DHA allows for quantum transfer and communication of π-electrons, which explains the precise depolarisation of retinal membranes and the cohesive, organised neural signalling which characterises higher intelligence.

1. Introduction

The cell membrane lipid bilayer is the home of about one third of all known cellular proteins. These are the transporters, ion channels, receptors and signalling systems, and are dependent on the lipid domains in which they sit. The species, organ and even sub-cellular specificity of lipids testifies to exact demands of differentiated cells and precise protein–lipid interactions. For example, the membrane lipid composition is different for the endothelium, heart muscle, kidneys, liver and brain. Even within a given tissue, there are specific differences in the plasma membrane compared to the mitochondria and nuclear envelope.

The highly specific, characteristic differences in the plasma membranes of the neural, endothelial and epithelial cells; or glomerulus and distal tubules of the kidneys, cannot be based on vague compositional directives. We propose this constancy and specificity is a function of specific protein–lipid interactions operating in a multi-dimensional fashion similar to what has been described for proteins. *This relationship has to be a two way system.* During cell differentiation, the specialist proteins that arrive will seek a lipid match and vice versa [1,2]. If the matching lipids are not present the system may fail, regardless of the protein components.

Proteins are built with 20 amino acids that are assembled into three-dimensional structures. Because of the molecular motion of the final protein assembly, it is an example of supra-molecular chemistry which includes reversible non-covalent associations, hydrogen bonding, metal coordination, π–π interactions and electrochemical effects involving lipophilic and hydrophilic structures. In that sense a protein in a living cell exists in six dimensions.

4th Dimension: electrochemical profile.

5th Dimension: van der Waals type forces.

* Corresponding author. Tel.: +44 772 525 0541; fax: +44 20 3315 3090.
E-mail address: michael.crawford@imperial.ac.uk (M.A. Crawford).

0952-3278/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.plefa.2012.08.005

6th Dimension: time. The time of occupancy of the state which optimises the probability of electron cohesion.

The van der Waals equation can be written as follows:

$$\left(p+\frac{a'}{v^2}\right)(v-b')=kT$$

where p is the pressure of the fluid, T is the absolute temperature, a' is a measure for the attraction between the particles and b' is the average volume excluded from v by a particle. This equation can be utilised to describe lipid properties: a' will vary with the chain length and degree of unsaturation. Chain length and saturation affect the pK of the acid, which in turn is a determinant of the lipid polarity. b' will also vary with physical chain length of the fatty acid (16–24 carbons) and degree of unsaturation (1–6 double bonds), as well as with lipid concentration—especially since lipids form micelles and other macromolecular structures in aqueous milieus. The degree of unsaturation is also responsive to T and p.

Therefore lipids are not just an oil phase separating two aqueous regions as is frequently depicted, but have physical, chemical and electromagnetic properties which are operating in cellular functions in multiple dimensions. The electrical properties of the phospholipid head group and ceramides (and possibly the entire lipid chain) can be considered to exist with the same principles as described for proteins, but with a stronger temperature and pressure variation and a larger number of possible constituents. The idea that lipids interact specifically with membrane proteins is not new [1–3].

2. DHA abundance controls brain size and function

Comparative evidence on brain composition gave us the first clue to consider both proteins and lipids in six dimensions, and that lipids may specify proteins just as proteins specify lipids. In some animals DHA (-*cis*-docosa-4,7,10,13,16,19-hexaenoic acid or C22:6n-3) is present either in the diet or as a product of the strongly rate limited synthesis from plant-derived α-linolenic acid (C18:3n-3) [4]. If the velocity of body growth is small then adequate synthesis of DHA for brain growth can occur, resulting in a brain/bodyweight ratio of $>2\%$ (e.g. small rodents). As the velocity of body growth or protein acquisition increases, the rate limitation of DHA synthesis dominates and relative brain size diminishes. In the largest land-based mammals the ratio shrinks to $<0.1\%$ (rhinoceros, Cape buffalo) despite abundant α-linolenic acid in the tissues.

An abundant source of preformed DHA, as in the diets of marine mammals, can obviate low biosynthetic capabilities. Such evidence suggests that nutrition, especially with regard to DHA, was a determinant of brain size. For example, the dolphin has a 1.8 kg brain, compared with a land based zebra of a similar bodyweight with only 360 g brain.

The rate limitation for DHA with its tortuous synthetic route to its synthesis requiring its import, metabolism and export from the peroxisomes [4], explains how very small mammals like squirrels with a high metabolic rate and a reasonably efficient biosynthesis achieve a maximally high brain to bodyweight ratio of 2.4%. Incorporation of (isotopically labelled) preformed DHA into the developing rat pup brain was found to be more than an order of magnitude greater than incorporation of DHA synthesised from α-linolenic acid [5]. Humans are much less capable; we can only count on about 1% conversion of α-linolenic acid to DHA [6]. Yet across all mammal species, brain size decreases logarithmically with increase in bodyweight with two exceptions—the dolphin and the human [7,8]. Clearly we were doing something different during our evolution.

Lipids play a key role in signalling [9] and DHA is involved in the expression of several hundred genes in the brain [10]. The genomic evidence [10] means that an abundant dietary source of preformed DHA, as provided in littoral habitats, would actually stimulate the evolution of the brain, and a lack of DHA would be restrictive [6–8,11–14]. What we were doing differently is that we were a *very* small group of individuals who consistently ate marine and lacustrine food sources [15]. The superabundance of DHA (and Zn, Cu, I, Se, protein etc.), with its irreplaceable role in neural cell signalling, allowed the synaptic evolution of self-awareness and symbolic thinking and behaviour. Thus began our *cultural evolution*, very much faster and pervasive than *biological evolution*: most cultural evolution is dependent on teaching and adaptation rather than pure innovation and hard genetic changes. Yet we remain essentially the same beings, dependent on DHA for 600 million years and unable to move towards a new and improved species without the raw material.

Quite apart from any technical arguments, the late Philip Tobias summarised the argument succinctly: "wherever humans were evolving, they had to have water to drink"![1] In other words we did not evolve—especially with our highly dependent infants and children—on the arid savannah.

3. DHA and the origin of vision and the brain

For the first 2.5 billion years of evolution, there was little change in prokaryote life forms, dominated by anaerobic algae and bacteria. Amino acids have been recovered from carbonaceous chondrite meteorites, which are nearly as old as the Solar System (4.6 billion years), so we can assume these life forms utilised proteins. However the synthesis of DHA requires 6 oxygen atoms for the introduction of the 6 double bonds; therefore it is unlikely that there was an abundance of DHA before oxidative metabolism evolved.

DHA is a major constituent of the signalling membranes of the brain and visual system. Indeed a study of the dynoflagelates, which have an eye spot, revealed to John Sergent and one of us (MC) the presence not only of DHA in the phospholipids but also di-DHA phosphoglycerides. This chemistry is the same for the photoreceptors of the cephalopods, fish, amphibia, reptiles, birds and mammals. The likely scenario is that instead of converting photonic energy to carbohydrates or proteins, DHA converted it to electricity and hence the evolution of the nervous system and ultimately the brain, where DHA is selectively incorporated into synapses [13].

Vision and the brain evolved in the sea. In all vertebrates so far studied, DHA is the major essential fatty acid constituent of the brain. The n-3 docosapentaenoic acid (*cis*-docosa-4,7,10,13,16-pentaenoic acid; C22:5n-33) and the n-6 DPA (*cis*-docosa-7,10,13,16,19-pentaenoic acid; C22:5n-6) differ from DHA by the absence of only one double bond (Fig. 1). They are thermodynamically easier to synthesise and less susceptible to peroxidation. Yet neither replaced DHA during 600 million years of evolution. *This is extreme conservation*. The preservation of DHA in neural signalling systems for 500–600 million years occurred despite enormous genomic changes since the beginning of animal evolution.

Although there is a wide variation in the chemistry of the liver and muscle of the animal species so far studied, there is little or no variation in the brain [7]. What varies is the extent to which it evolved or rather its size and complexity relative to the demands of the body. Although arachidonic acid (20:4n-6, AA) is also

[1] At a joint conference of the Institute of Brain Chemistry and Human Nutrition and the McCarrison Society: *A New Light on Human Origins*, The Zoological Society Meeting Room—Regents Park, London [22nd September 2000].

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

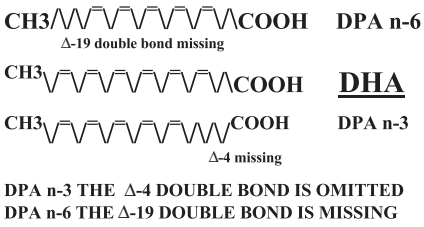


Fig. 1. Although n-3 DPA is a precursor for DHA neither DPA replaced DHA in 600 million years of evolution. The full sequence of six methylene-interrupted double bonds may be critical to the role of DHA in signalling membranes.

required for neural membranes, it is more readily synthesised and abundant in land-based foods. There is a determinacy between the more limiting DHA and the evolution of the brain [8,14]; almost any human diet with enough DHA will necessarily have enough AA or its plant precursor linoleic acid (18:2n-6).

This extreme conservation implies that the DHA was actually dictating to DNA rather than the more conventional view of evolution occurring the other way round. That is, despite countless mutations that might have occurred, any that sought to replace DHA with a DPA or another molecule did not work. In that sense, DHA was the master of DNA.

Whilst the view that nutritional conditions had a role in directing evolution seems contrary to the gene-centric view of evolution, it is consistent with pure Darwinism. In "*The Origin of Species*" Darwin declared there were two forces in evolution, Natural Selection and Conditions of Existence [16]. He considered the latter the more powerful. This aspect of Darwin's thesis was considered too Lamarckian by Weismann [17] and it was more or less abandoned. Marsh [18] emphasises that in all six editions of "Origin" Darwin repeats his claim on the Conditions of Existence. Indeed, Darwin spent much of the rest of his life searching for what he called "Pangenes" in the blood which could translate information from the environment to the genome. Darwin's Pangenes are now understood as reverse transcriptase and the entire field of Epigenetics. We suggest that DHA is a Condition of Existence that made it the master of DNA since the beginning of animal evolution. If you like it was the "selfish DHA" not DNA that ruled the evolution of vision and the brain.

3.1. What is special about DHA?

The curious facet of DHA dominance in evolution is that its DPA precursor differs by only two protons and would have been more readily available. The difference in fluidity between DHA and DPA is very small; certainly not enough to explain 600 million years of conservation of DHA in photoreception and neural signalling systems. Alternatively, Bloom and colleagues suggested that DHA might have unique electromagnetic properties which have little to do with membrane fluidity [19].

Gawrisch and colleagues have also attempted to explain the DPA/DHA paradox. Using solid-state NMR measurements and molecular simulations they provide an image of DHA as a uniquely flexible molecule with rapid transitions between large numbers of conformers on the time scale from picoseconds to hundreds of nanoseconds [20]. The low barriers to torsional rotation about C–C bonds that link the *cis*-locked double bonds with the methylene carbons between them are responsible for this unusual flexibility. Both the amplitude and frequency of motion increase towards the terminal methyl group of DHA. Like us, these authors understand that classical biophysics does not have a ready explanation for the irreplaceable DHA.

4. DHA and quantum mechanics

4.1. Energy minimised structures and quantum communication

The van der Waals equation hints that DHA will have both stereochemical and electromagnetic properties. Quantum mechanics can predict the existence of energy levels inside lattices, whereby any electron in that level can be effectively spread across the whole structure, thus becoming a quasi-particle or a wave. Albert Szent-Gyorgyi postulated that common energy levels could exist in protein structures, as they contained "a great number of atoms, closely packed with great regularity". He considered the communication of energy between molecules in biological systems could be achieved through coherence of electrons raised to a higher energy state. The formation of a triplet state of the π-electrons around double bonds in aromatic amino acids was the basis for this mechanism [21,22].

Since Szent-Gyorgyi, the electron transfer of the energy production system in mitochondria has become well known. Bendall [23] considered the conformal dynamics of proteins to be reliant on the long range transfer of electrons. The method of transport is quantum mechanical tunnelling, a feature of proteins demonstrated by Hopfield [24]. Hackermuller et al. [25] obtained evidence that tetraphenylporphyrin exhibits wave like behaviour, indicating quantum coherence in nature.

Hammeroff and Penrose [26] proposed a model based on quantum mechanics that can explain consciousness and is testable. In the "Orchestrated Objective Reduction" model of consciousness, quantum coherence exists in the microtubules found in neurons. It is hypothesised that microtubules are capable of quantum computing, and quantum computations are translated to classical outputs—hence consciousness. Hammeroff [27] then proposed the connections between neurons were linked to consciousness. Gap junctions are small enough for quantum objects to cross by quantum tunnelling, allowing cohesion across regions of the brain and creating consciousness.

The brain can contain numerous proteins but is absolutely dysfunctional without DHA and AA. We hypothesise that the π-electrons in DHA could behave in similar quantum manner, explaining the unique and irreplaceable role of DHA in neuronal signalling. We must also consider that beyond consciousness, cohesion across regions of the brain drove the evolution of symbolic thinking and behaviour, which is the hallmark of humanity.

5. Electron coherence in DHA

Crawford et al. [28] proposed a possible mechanism whereby photoreceptor membranes could be responsible for the electrical current seen in this system by Jin et al. [29]. DHA is present in greater than 50% of the outer rod segment membrane phosphoglycerides, with some phosphoglycerides containing two DHA molecules. Crawford et al. [28] postulated that the π-electrons of the double bonds are confined to potential wells by the intervening methyl groups. Confinement can lead to stationary states: if these states couple, then common energy levels predicted by Szent-Gyorgyi could exist. Arguing against this idea is the principle that double bonds form "kinks" in the lipid carbon chain, and non-planar lattices can have very high electrical resistance. However molecular dynamic assessment shows that three of the DHA double bonds are planar, which has implications for electron coherence.

The planar structure of the energy-minimised DHA conformation is a fundamental characteristic of six double bonds separated by $-\mathbf{CH_2}-$ groups (Fig. 2). If there are only five (e.g. DPA), the

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

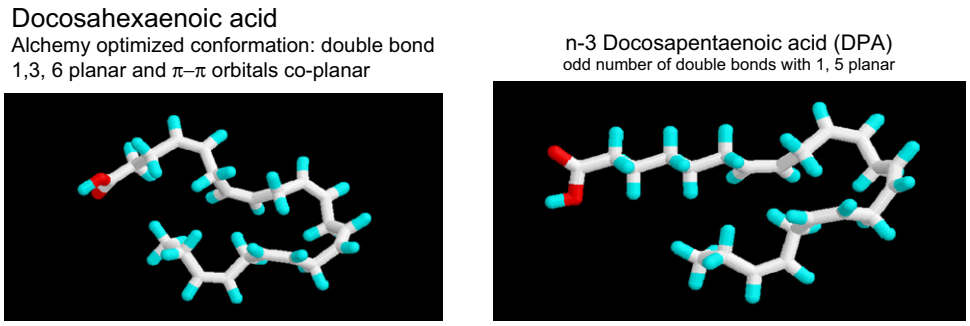


Fig. 2. The planar structure of the preferred DHA conformation is a fundamental characteristic of the six double bonds separated by CH_2 groups. If there are only five, the corresponding molecule cannot be made planar.

corresponding molecule cannot be made planar. With three of the double bonds co-planar, parallel alignment with another planar molecule can occur.

The π bonds always have a **(+ve)**−end and a **(−ve)** end, i.e. a directionality at the molecular level. The shape of their probability orbits will lean towards a **(+ve)** end of a dipole moment. Thus three coplanar double bonds immediately have at least two different potential energy states: two with the π bonds up or three with the π bonds up (and the mirror image of two down or three down).

Structurally the other three double bonds are not symmetrical. Two are above the plane, one below. It is not possible for DHA to be symmetrical molecule because the π bond field effects are always unequal. Absorbance of a quantised amount of energy is precisely that amount which will flip the direction of bond polarity to the opposite direction [30]; release of essentially the same amount of energy is the return to the initial polarity. DHA with one **CH═CH** below the plane and one above is not polarised. But with two **CH═CH** groups on the same side, there is a net polarisation to the whole molecule. Hence if the **CH═CH** group flips it will turn on polarisation of the molecule and flipping back turns it off. The length of time it takes to flip is presumably the length of time of visual memory. "Flipping" in response to incoming light is the basis of the photon energization of retinal.

In addition, each of the **CH_2** hydrogens in **–CH_2–CH═CH–CH_2–** have an unequal charge density, corresponding to above or below the **–C–CH═CH–C–** π bonds which lie perfectly flat at the molecular scale. Given a dipole across the molecule, the π bonds will have partial positive charge up **(δ+Ve)** whilst the **CH** on the same side of the plane will correspondingly be slightly negative **(δ-Ve)**. So in a sequence of double bonds as in DHA, the sign of partial charges alternate ….**δ(+Ve).. δ(–Ve)**… **δ(+Ve).. δ(–Ve)** (Fig. 3).

In this conformation (geometrically best packed/lowest energy) the second **CH═CH** group at the carboxyl end is in effect upside down and the signs of the partial charge on the **–CH_2–** groups next to it are opposite those of the other two adjacent **CH═CH** pairs. Thus the energy barrier [moment of inertia] to flip the second **CH═CH** group is lower than that of any other **CH═CH** group. The arrangement of the double bonds with this **CH═CH** group flipped creates a conformation similar to conjugated double bonds, and conjugated double bonds can store energy in the ultraviolet to visible range, which is the range of vision across species.

Extended Hückel calculations (Hyperchem) describe the distribution of the π-electron clouds to be uniformly distorted with the π bond energy different above and below the plane. Interestingly, molecular dynamics modelling (Hyperchem) show the electrons of the **–CH_2–** groups also exhibiting a similar polarisation. With the π-bond energy distributed above and below the plane of the molecule and polarisation of the **–CH_2–** intervening groups, the outer orbit electrons could communicate in a way

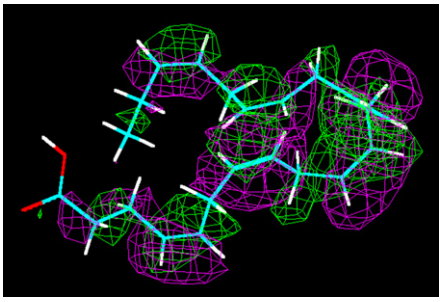


Fig. 3. Molecular dynamic representation of DHA illustrating the alternative δ−ve and δ+ve distribution through the molecule. With the electrons in the methylene groups participating, a probability exists of electron cohesion across the whole molecule. The methylene participation is confirmed in the NOE analysis described later.

leading to conduction. In other words, there is a probability of coherent communication between two π-electron sets on either side of a **–CH_2–** which could include the participation of the methylene group and electron tunnelling [31]. Cohesion could conceivably extend along the whole molecule, but would be less probable if one of the double bonds is removed as the methylene interruption becomes a propene interruption.

The classical problem with DHA as a conductor is that the methylene interruption of the π-electrons prevents the "copper wire" electron transfer as in a conjugated sequence **(–CH═CH–CH═CH–CH═CH–)** in retinal or the aromatic ring. DHA then becomes an electrical resistor or barrier. Hence the properties of the **–CH_2–** groups become critical. In classical physics, no current can pass and there can be no communication between double bonds unless the energy across the molecule overcomes the **–CH_2–** methylene barrier. With quantum mechanical theory, communication can occur as evidenced in semiconductors, but certain parameters must be met. We will show that DHA has conformations and energy states that meet theoretical parameters for coherence.

5.1. Photoreception

The outer segment of the photoreceptor encloses a stack of disc shaped membranes. These discs contain many transmembrane proteins called opsins. The membrane lipid is packed with >50% DHA and even some very long chain (C30+) hexaenoic phosphoglycerides. Each opsin molecule is associated with a smaller chromophore molecule called retinal. In rod cells this system is called rhodopsin [32].

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

Retinal can exist in a number of different forms; however the main isomers are 11-*cis* to all *trans*-form. When an incident photon strikes the photoreceptor, isomerisation of retinal goes from the 11-*cis* to all-*trans* form. The energy of the photon is transferred to a π-electron, raising it to a higher energy state. This excitation "breaks" the outer π aspect of the double bond, which becomes a single bond, leaving the carbons free to rotate. With recapture of the electron, the double bond reforms into the *trans*-configuration. The conjugated double bond sequence of retinal is capable of transporting electrons like a copper wire as the π-electron clouds are in close proximity and can overlap. Hence the shift might act like an electric on/off switch: one wonders if isomerization might halt electron flow and arrest the dark current identified by Jin et al. [29].

When rhodopsin has been activated it is called metarhodopsin. Experiments have shown that the initial response to a flash of light is highly amplified [32]. The formation of metarhodopsin triggers a G-protein activation cascade that amplifies the signal many fold. These cascades are similar to other G-protein-coupled signalling, but with important differences. Usually activation occurs when a receptor protein binds to another molecule. However in case of a photoreceptor the retinoid is already bound to a receptor. Secondly, photoreceptor rods have a standing current in the dark-adapted state. The dark current keeps the membrane potential in its resting state of -40 mV. Light activation leads to arrest of the dark current and membrane hyperpolarization [32].

The cascade of events that leads to the closing of cGMP gated ion channels is well-documented. The reduction in cGMP closes the ion-gated channels in the outer segment. The inner segment has potassium channels that are constantly open. Hence with the outer ion channels closed, the potassium ions accumulate, and being positive cause the hyperpolarization. Then at a precise value of -70 mV the potential depolarises, and that is the signal. Far less is known about the mechanism that causes the depolarisation of the cell membrane; even less about its absolute precision.

The number of steps in depolarisation is contested. At one end of the spectrum some researchers favour a reverse cascade that eventually shuts down metarhodopsin; at the other end some believe it is a single massive event. The classical view of phototransduction involves activation of G-proteins for which thus far there is no quantum-specific evidence—yet depolarisation occurs at a precise energy level of -70 mV. Without such precision, three-dimensional and peripheral vision would be compromised and there would be extensive loss of visual acuity. Not surprisingly, the universal finding in DHA deficiency is a loss of visual acuity [33,34], indicating any quantised effect is to be found in the lipids or the lipid-protein interaction and not the G-protein.

5.2. A quantised visual signal

As described above there is a surprising planarity to the DHA molecule and a **δ (+)ve** to **δ (−)ve** polarisation to the electron cloud. The same polarisation applies to the sigma electrons around the methylene groups. In the photoreceptor membrane, the polar head group on the outer face is dominated by a phosphate and a strong quaternary amine (choline). On the inner side there is the same phosphate but a weak primary amine (ethanolamine). The bilayer in its resting state will be charged, with the probability of finding an electron greater in the direction of choline. There are two conditions which could pull an electron out of DHA (i) a sufficient electrical charge as in hyperpolarization and (ii) the Einstein photo-electric effect; neither is mutually exclusive.

If one electron is delocalised and pulled out by hyperpolarization, an immediately distal electron will take its place and this electron tunnelling would lead to a current to flow. The Pauli exclusion principle tells us that no two electrons can occupy the same energy state. If one electron is pulled out, the loss leaves a hole which can only be filled by an incoming electron of the same quantum status of spin and energy (Fig. 4). Hence we have a plausible explanation for the *absolute precision* of the depolarisation and the high degree of visual acuity. This process could theoretically depolarise the membrane and moreover do so only at a quantised energy level.

Hopfield [24] described this process of electron tunnelling in proteins. The possibility of finding an electron distant from its usual orbital falls off exponentially with distance. Hopfield calculated the distances over which tunnelling could occur, finding that the limit was about 8 Å (Fig. 5) The distance in methylene interruption is less than 6 Å, making the electron tunnelling transfer between the π-orbitals feasible throughout DHA. The possibility fails if one double bond is removed and replaced by a saturated chain as in the DPAs.

The electrons will only jump the energy barrier at a precise energy level El and no other. If the photon input is increased where E2 > El or E3 ⩾ El the electrons still go through at El. At an energy level < E1 nothing will happen. If E3 was very large, one might expect an "after glow" image but the signal will be at E1.

Electron tunnelling would explain currently unexplained phenomena in the visual system: (1) How is the system capable of responding to signals that vary in intensity by a factor of 10^5?, and (2) why does activation always produce an identical electrical response regardless of input? Note the involvement of DHA in depolarisation can still operate with the presently accepted ionic movement and the G-protein activity.

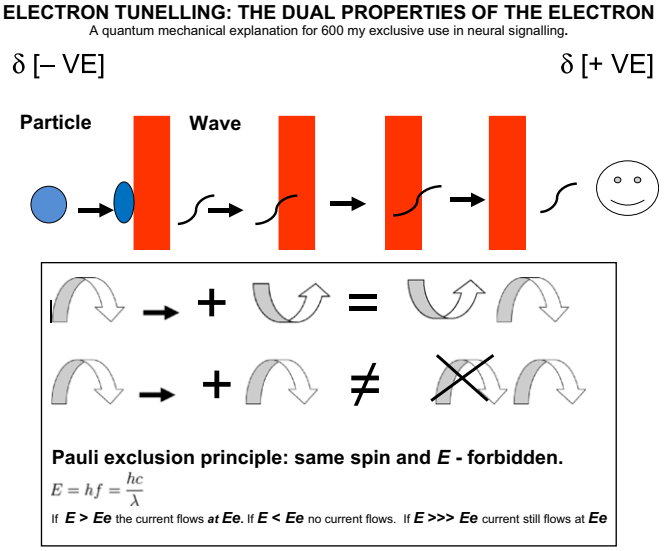


Fig. 4. The dual particle/wave properties of an electron explain tunnelling. Seen as particle it is like a ball hitting a brick wall—impossible to penetrate. However there is no such thing as a ball or brick wall; the electron's "position" is only the sum of the molecular electromagnetic forces defining a probability function for its location. As a wave, there are probability distributions in which the electron penetrates barriers and can communicate with neighbouring molecules or end up in other regions of the molecule. Removal of an electron in a neighbouring orbit will reduce repulsive forces and invite the electron into a new, higher-energy orbit. An electropositive charge will increase the probability of occupation. The π-electrons have opposite intrinsic angular momentums or spin. The occupation of the orbit by two electrons with the same quantum energy state is forbidden. The Pauli exclusion principle ensures that the energy level at which tunnelling occurs is precise.

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

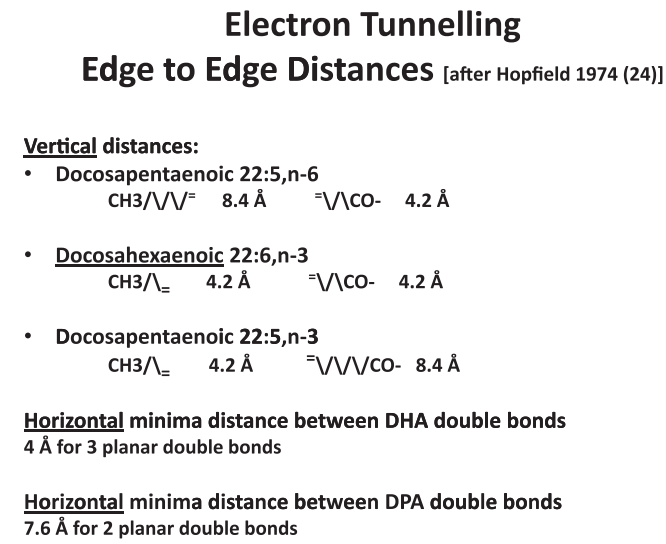


Fig. 5. The distances across DHA come within the range where tunnelling is reasonably probable Ref. [24]However, if a double bond is replaced by a single bond the resulting distance has a very low probability.

6. Is a conduction band feasible in DHA?

6.1. The Kronig Penney model

To test this idea further we have examined Kronig Penney Model.[2] The long range transfer of electrons inside proteins is reliant on the tunnelling effect [24,35]. One of the issues that makes tunnelling so hard to predict and\or observe directly is that the nuclear configuration changes constantly, as do the electronic configurations of the donor and acceptor states. Nonetheless, at times of resonance, electrons localised on the donor site will tunnel over to the acceptor site [36].

Another problem is finding the tunnelling pathway. If we call the resonance state the bridge state, then by definition, as the nuclear and electronic configurations fluctuate, no bridging state will be permanent [31]. Tunnelling from the donor state decays exponentially, however electron transfer has been observed experimentally for distances of 15–30 Å, too far for a decaying wave function to reach. It is therefore believed that in some situations there is an organic intermediate that facilitates tunnelling [31]. However, in DHA whilst a bridging state may be unattainable in many conformations, there will be some in which coherence becomes feasible.

Jin et al. [29] described quite amazing conduction properties of bacteriorhodopsin. An isolated patch of purple membrane had two gold contacts attached, then an electrochemical gradient was applied across it. Although the membrane is an insulator a small current of 0.7 nA was measured. When the gold contacts were illuminated by green light, the current jumped to 1.7 nA. Jin et al. [29] were able to pinpoint the source of the current; it was the transmembrane protein bacteriorhodopsin. When the green light ceased, the current was seen to persist across the membrane, only returning to its initial value some 2 or 3 min later. No explanation for this phenomena could be found, indeed it was stated that "the biological processes responsible were so well hidden that we have not found them".

As discussed previously the three coplanar bonds of DHA would not be a typical conjugated system. Methylene group interruptions would present a potential barrier to the π-electrons, hence leading to confinement, but confinement leads to the elusive quantisation.

Abstracting a simple model of a periodic lattice for the three coplanar bonds, it is straightforward to apply the Kronig–Penney model (see Razavy [35]). The resulting functional energy equation is

$$\frac{\beta^2-\alpha^2}{2\alpha\beta}\sinh(\beta b)\sin(\alpha a)+\cosh(\beta b)\cos(\alpha a)=\cos(k[a+b]) \quad (1)$$

where b is the well width, a is the barrier width and k is the wave vector. Both QUOTE and β are of the form, $\alpha=\sqrt{2mE}/\hbar$ and $\beta=\sqrt{2m(V-E/\hbar}$, where m is the mass of the electron, V is the barrier height and E is the energy of the particle in the well. The left hand side is the functional, and denoted as $F[E]$.

The barrier distance in the three coplanar double bonds is 4 Å; also the average carbon double bond length is ~1.33 Å. Inserting these values into equation 1, it should be possible to investigate if, under these parameters, any conduction band can form. Both of the following graphs (Figs. 6 and 7) were plotted using the excellent Matlab based tool developed by [36].

The final puzzle is determining barrier height for the **–CH_3–**. This is not a straightforward matter due to its rotation states [38]. However if we look at the equation of the Kronig–Penney Model above, we see that we only deal with differences between barrier height and the range of energies for conduction band formation. Hence any value for the π-electrons are relative to the barrier. Therefore we can let the ground state of the π-electrons be zero, and have the barrier height 5 eV above it. The above calculation shows that theoretically, at least one conduction band can form. To satisfy this hypothesis we only *need* one.

6.2. Photoelectric effects

The above argument considers an electrochemical potential across the membrane as the motive. However, the photoreceptor is bombarded by photons. The Einstein photoelectric effect could also play a role in phototransduction. The isomerisation of the 11-*cis* retinal is achieved by the energy of a photon exciting a π-electron into an escape mode. The energy of a photon in visible wavelengths is more than sufficient to eject an electron from retinal, could the same photoexcitation take place in the π electrons of DHA?

The DHA double bonds consist of a σ bond and a π bond. By subtracting 80 kcal/mole (the σ bond energy) from 145 kcal/mole (the **C=C** bond energy) we calculate that the π bond has a dissociation energy of about 65 kcal/mole. This is much less than the σ-bond energy, and therefore π bonds are more reactive than σ bonds. This means that, all things being equal, the π bonds of DHA are more likely to undergo activation by light.

In the geometrically best packed/lowest energy conformation, the second **CH=CH** group is in effect upside down and the sign of the partial charge on the CH_2 groups to it are opposite to that of the two adjacent **CH=CH** pairs. Thus the energy barrier [moment of inertia] to flip this **CH=CH** group is lower than that of any other **CH=CH** group [37].

The arrangement of the double bonds with this **CH=CH** group flipped creates a conformation similar to conjugated double bonds (Fig. 8), which can store energy in the ultraviolet to visible range. From molecular dynamic calculations the ground state energy of DHA is 50 kJ/mol which is in the region of photoreception. It is interesting that visual responses still can be detected in the electroretinograms of "mice lacking critical components of all known retinal phototransduction cascades" [39]. Excitation of a π-electron in the DHA phosphoglycerides followed by electron tunnelling in response to hyperpolarization could offer a theoretical solution. This view fits with that of Gawrisch et al. [20] who describe low barriers to torsional rotation about the **C–C** bonds

[2] Largely due to the Masters thesis by MG.

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

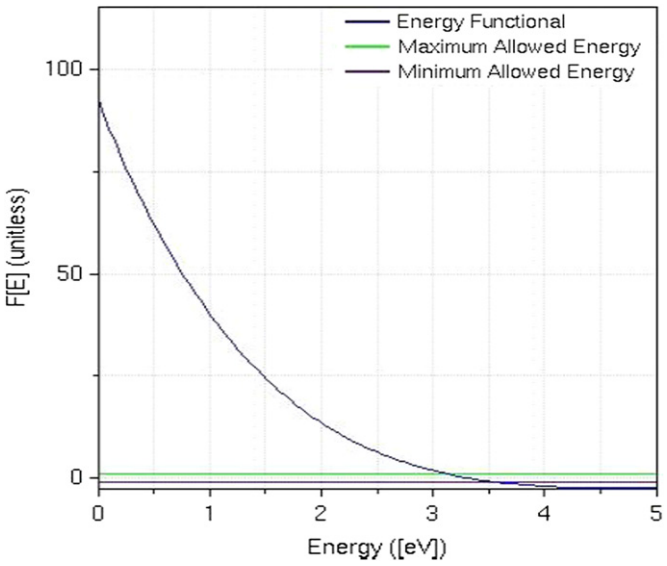
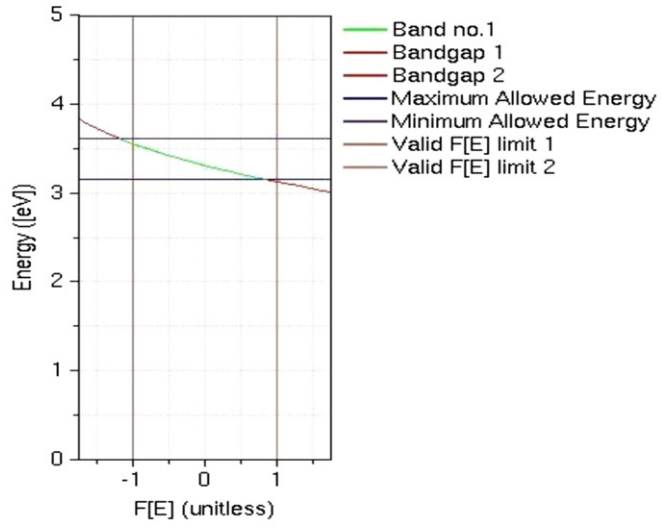


Fig. 6. The energy functional $F[E]$, is plotted against the energy difference between the ground state of the π electrons and the height of a confining potential step barrier. The maximum and minimum values of the energy functional are also plotted. If $F[E]$ exists in this region, then the Kronig–Penney predicts the possibility of energy band formation.



Band Information

Band Index	Emin [eV]	Emax [eV]	Bandwidth [eV]	Bandgap [eV]
1	3.157	3.612	0.455	----

Fig. 7. The allowed energy band is shown in green. Any value outside of the closed interval. [−1,1]. is not considered by the Kronig–Penney model.

that link the *cis*-locked double bonds with the methylene carbons between them.

6.3. The curious upside-down receptor

Common sense would dictate that the photoreceptor would face the incoming photons. Curiously, this is not the case. Instead their face is buried in the retinal reticulo-endothelium and the back end faces the incoming stream of photons. Again classical biophysics has no ready explanation for this [32]. However, the upside-down arrangement might be determined by a quantum mechanical property, the particle–wave duality of photons. Incoming light hits the back end of the photoreceptors and has to squeeze through the slits between the cell structures. This may split the light into a wave form interference pattern as in Young's double slit experiment. Acting as a wave, the incoming photon has a far better chance of activating the very specific location of the retinal *cis*-double bond than as a discreet particle which could easily miss such a small target.

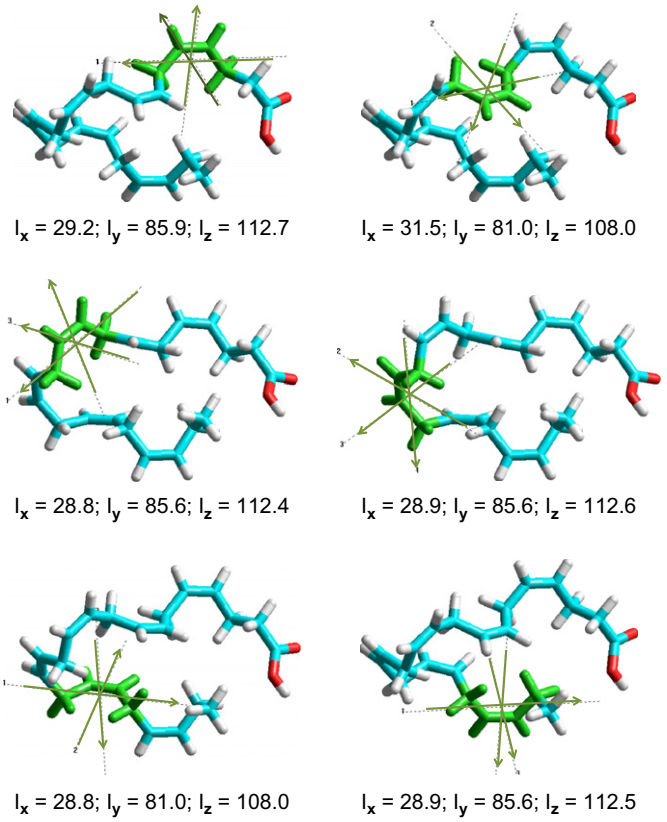


Fig. 8. Moments of inertia across the DHA double bonds.

A photon wave form also raises the question as to whether or not the incoming wave could activate retinal and DHA simultaneously. Visible light ranges from about 380 to 740 nm; the distance between the retinal and the DHA phosphoglycerides is within this range. Although it is unlikely that there is sufficient energy for a photon to energise both retinal and DHA electrons simultaneously, more than one photon is usually involved in what we see. This situation raises the possibility of cohesion between the retinoid and DHA π-electron activation.

In this theory, the energy released in the signalling would be absolutely and precisely quantised by tunnelling, giving us the clear vision, high acuity necessary for reading, fine motor skills, and three-dimensional vision; together with smooth mental processing of our external environment upon which we depend. A similar process might take place in the synapse where the DHA is also densely packed. There DHA might act as a quantum gate controlling the signal in a fashion reminiscent of semi-conduction.

7. Nuclear overhouser enhancement

To test the electromagnetic properties of π-electrons and the **–CH_2–** groups in DHA we studied its behaviour in a magnetic field.

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

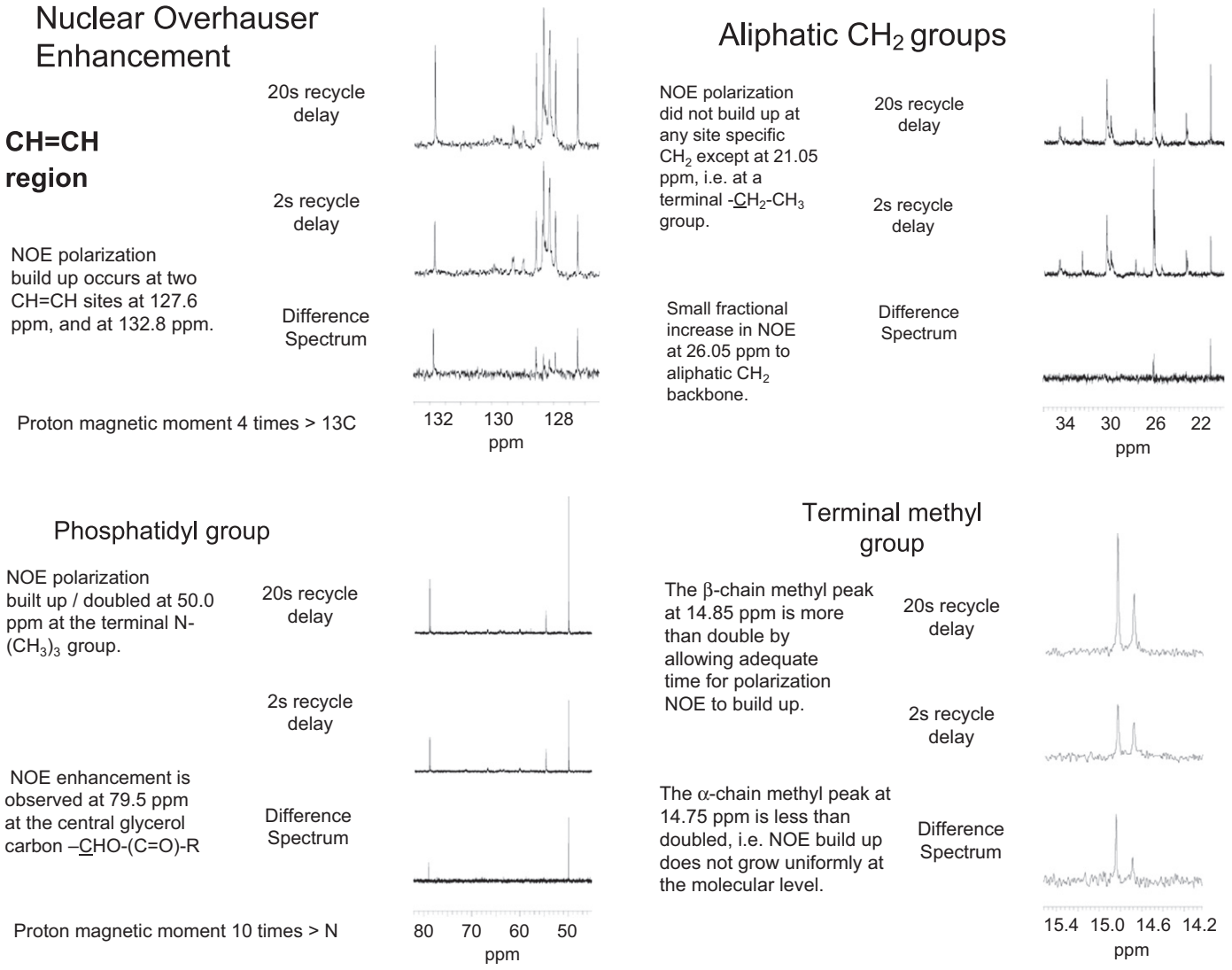


Fig. 9. The nuclear overhauser effect can be seen in NMR spectra when the magnetic polarity is reversed. The intrinsic angular momentum of polarisable elementary particles will align with a given direction in a magnetic field. If a region of a molecule has an electron distribution which is polarisable that will respond to polarity reversal and is detectable by subtracting the two spectra. It can be seen from NOE spectra of DHA that the polar head group (as expected), methylene group (unexpected), double bond (expected) and terminal methyl (unexpected) responded to reversed polarity.

We used the Nuclear Overhouser Enhancement (NOE) technique whereby the molecule is exposed to an NMR magnetic field. The magnetic field is then switched to the opposite polarisation [40,41]. If there is no response the spectra are identical at both polarities. If there is a response, the subtracted spectra record the electromagnetic activity in specific region(s) of the molecules.

Fig. 9 illustrate the response of DHA in which the planar double bonds, and critically, the **–CH_2–** groups, the polar head groups and surprisingly the terminal methyl display activity.

8. Conclusion

As far as our knowledge goes, DHA has been the dominant fatty acid in the membrane phosphoglycerides of the photoreceptors, neurones and synapses for all 600 million years of animal evolution. Even today, the composition of the photoreceptor and brain varies little between species despite large scale species variation in the lipid composition of the diet, liver and muscle. This consistency is despite the fact that its DPA precursor, which differs by only two protons, is more readily available, requires significantly less energy to synthesise, and is more resistant to peroxidation. Moreover, the difference in membrane liquidity by substituting DPA is minimal. By contrast over 600 million years animal genomes underwent countless mutations with enormous variation in protein composition and structures.

We suggest that DHA is one Darwin's "Conditions of Existence" which made DHA the master of DNA since the beginning of animal evolution. Proteins are selected to function with the constancy of DHA: it was the "selfish DHA" not DNA that ruled the evolution of vision and the brain. We propose protein–lipid interactions operate in a multi-dimensional fashion similar to what has been described for proteins. This relationship has to be a two way system. During cell differentiation, the specialist proteins that arrive will seek a lipid match and vice versa. If the matching lipids are not present the system may fail.

A practical point is that random mutation and selection for survival have little predictive power. However, has powerful predictive power because it predicts human biological evolution slows or reverts if DHA is not superabundant. As we move inland and consume mostly agricultural-based processed foods, we can expect global nutrition crises. We have these now in terms of

Please cite this article as: M.A. Crawford, et al., A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signalling throughout evolution, Prostaglandins Leukotrienes Essent. Fatty Acids (2012), http://dx.doi.org/10.1016/j.plefa.2012.08.005

obesity and Type II diabetes, but the less obvious crisis is mental ill-health. Mental ill-health is now the mostly costly segment of health care in the West and pathologies are becoming globalised.[3]

The extraordinary conservation and irreplaceable nature of DHA in neuronal signalling and its high concentration in the photoreceptor can be explained if it functions as an electron tunnelling device providing quantised signals. Quantum mechanical treatment explains the *absolute precision* of the membrane depolarisation in phototransduction. This precision is essential to visual acuity and synaptic signalling. Quantum mechanics also explains the photoreceptor oriented counter-intuitively away from incoming light.

We have established that energy minimised structures, molecular polarisation and moment of inertia allow for the theoretical possibility of DHA operating in the realm of supra-molecular chemistry with electron quantum coherence but we clearly acknowledge that further investigation is required.

Acknowledgements

We wish to thank the Letten and Mother and Child Foundations for their support. We are also grateful to the Uganda Game Department, Makerere Medical College and the Zoological Society of London for their contribution to the initial evidence for the significance of DHA in the evolution of the brain. This paper is in recognition and memory of the late Philip Tobias whose support following his Dual Congress of Paleoanthropology and Biology, in Sun City, South Africa 1998 was an important stimulus to persevere with this story.

References

[1] F. Dumas, M.C. Lebrun, J.F. Tocanne, Is the protein/lipid hydrophobic matching principle relevant to membrane organization and functions? FEBS Lett. 458 (3) (1999) 271–277.
[2] M.M. Sperotto, O.G. Mouritsen, Lipid enrichment and selectivity of integral membrane proteins in two-component lipid bilayers, Eur. Biophys. J. 22 (5) (1993) 323–328.
[3] C. Song, H. Holmsen, W. Nerdal, Existence of lipid microdomains in bilayer of dipalmitoyl phosphatidylcholine (DPPC) and 1-stearoyl-2-docosahexenoyl phosphatidylserine (SDPS) and their perturbation by chlorpromazine: a 13C and 31P solid-state NMR study, Biophys. Chem. 120 (3) (2006) 178–187.
[4] H. Sprecher, Metabolism of highly unsaturated n-3 and n-6 fatty acids, Biochim. Biophys. Acta 1486 (2–3) (2000) 219–231.
[5] A.J. Sinclair, Long-Chain Polyunsaturated FA in the Mammalian Brain, in: Proceedings of the Nutrition Society, 1975, 34, pp. 287–291.
[6] J.T. Brenna, N. Salem Jr, A.J. Sinclair, S.C. Cunnane, Alpha-linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans, Prostaglandins Leukot. Essent. Fatty Acids 80 (2–3) (2009) 85–91, International Society for the Study of Fatty Acids and Lipids (ISSFAL).
[7] M.A. Crawford, M. Bloom, C.L. Broadhurst, W.F. Schmidt, S.C. Cunnane, C. Galli, K. Ghebremeskel, F. Linseisen, J. Lloyd-Smith, J. Parkington, Evidence for the unique function of DHA during the evolution of the modern hominid brain, Lipids 34 (2009) S39–S47.
[8] C. Leigh Broadhurst, Y. Wang, M.A. Crawford, S.C. Cunnane, J.E. Parkington, W.F. Schmidt, Brain-specific lipids from marine, lacustrine, or terrestrial food resources: potential impact on early African *Homo sapiens*, Comp. Biochem. Physiol. Part B 131 (4) (2002) 653–673.
[9] A. Chawla, J.J. Repa, R.M. Evans, D.J. Mangelsdorf, Nuclear receptors and lipid physiology: opening the X-files, Science 294 (2001) 1866–1870.
[10] K. Kitajka, A.J. Sinclair, R.S. Weisinger, H.S. Weisinger, M. Mathai, A.P. Jayasooriya, J.E. Halver, L.G. Puskas, Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression, Proc. Natl. Acad. Sci. USA 101 (30) (2004) 10931–10936.
[11] A. Hardy, Was man more aquatic in the past? New Sci. 7 (1960) 642–645.
[12] E. Morgan, The Aquatic Ape Hypothesis, Souvenir Press, London, 1997.
[13] H. Suzuki, S. Manabe, O. Wada, M.A. Crawford, Rapid incorporation of docosahexaenoic acid from dietary sources into brain microsomal, synaptosomal and mitochondrial membranes in adult mice, Int. J. Vitam. Res. 67 (1997) 272–278.
[14] M.A. Crawford, A.J. Sinclair, Nutritional influences in the evolution of the mammalian brain, in: K. Elliot, J. Knight (Eds.), Lipids, Malnutrition and the Developing Brain, Elsevier, Amsterdam, 1972, pp. 267–292, A Ciba Foundation Symposium.
[15] C.W. Marean, Pinnacle pint cave 13B (Western Cape Province, South Africa in context: the cape floral kingdom, shellfish and modern human origins, J. Hum. Evol. (2010) 425–443.
[16] C. Darwin, On the Origin of Species by Means of Natural or The Preservation of Favoured Races in the Struggle for Life, 6th ed, John Murray, London, 1872.
[17] A. Weismann, All sufficiency of Natural Selection, Contemp. Rev. 64 (1893) 309–338.
[18] D. Marsh, Darwin's passionate environmentalism or the dangerous fallacy of the 'All-sufficiency of natural selection', Nutr. Health 21 (1) (2012) 76–90.
[19] M. Bloom, F. Linseisen, J. Lloyd-Smith, M.A. Crawford, Insights from NMR on the Functional Role of Polyunsaturated Lipids in the Brain. In: Magnetic Resonance and Brain Function—Approaches from Physics, Proceedings of the 1998 Enrico Fermi International School of Physics, Enrico Fermi Lecture, Course #139, Varenna, Italy, 1999, pp. 1–27, Editor B. Maraviglia.
[20] K. Gawrisch, N.V. Eldho, L.L. Holte, The structure of DHA in phospholipid membranes, Lipids 38 (4) (2003) 445–452.
[21] R.H. Steele, A. Szent-Gyorgyi, On excitation of biological substances, Proc. Natl. Acad. Sci. 43 (1957) 478–491. (Biochemistry).
[22] J. Avery, Z. Bay, A. Szent-Gyorgi, On energy transfer in biological systems, Proc. Natl. Acad. Sci. 47 (1961) 1742–1744, Biochemistry.
[23] D. Bendall, Interprotein Electron Transfer, in: D.S. Bendall, (Ed.), Protein Electron Transfer, Bios Scientific Publishers, Oxford, UK, 1996, pp. 43–68.
[24] J.J. Hopfield, Electron transfer between biological molecules by thermally activated tunneling, Proc. Natl. Acad. Sci. USA 71 (1974) 3640–3644.
[25] L. Hackermüller, S. Uttenthaler, K. Hornberger, E. Reiger, B. Brezger, A. Zeilinger, M. Arndt, M. Wave, Nature of biomolecules and fluorofullerenes, Phys. Rev. Lett. 91 (2003) 090408.
[26] S. Hameroff, R. Penrose, Quantum computation in brain microtubules the Penrose-Hameroff Orch OR model of consciousness, Philos. Trans. R. Soc. London A 356 (1998) 1869–1896.
[27] S. Hameroff, The conscious pilot-dendritic synchrony moves through the brain to mediate consciousness, J. Biol. Phys. 36 (1) (2010) 71–93.
[28] M.A. Crawford, C.L..Broadhurst, C. Galli, K. Ghebremeskel, H. Holmsen, L.F. Saugstad, W.F. Schmidt, A.J. Sinclair, S.C. Cunnane, The Role of Docosahexaenioc and Arachidonic Acids as Determinants of Evolution and Hominid Brain Development, Fisheries for Global Welfare and Environment, 5th World Fisheries Congress, 2003, pp. 57–76.
[29] Y. Jin, T. Honig, I. Ron, N. Friedman, M. Sheves, D. Cahen, Bacteriorhodopsin (bR) as an electronic conduction medium: current transport through bR-containing monolayers, Chem. Soc. Rev. 37 (11) (2008) 2422–2432.
[30] D. Casanova, M. Head-Gordon, Restricted active space spin-flip configuration interaction approach: theory, implementation and examples, Phys. Chem. Chem. Phys. 11 (42) (2009) 9779–9790.
[31] A. Stuchebrukhov, A long_distance electron tunneling in proteins: a new challenge for time resolved spectroscopy, Laser Phys. 1 (2010) 125–138, ISSN 1054_660X.
[32] M.E, Burns, T.D. Lamb, Visual Transduction by Rod and Cone Photoreceptors, in: L. Chalupa, J. Werner, (Ed.), The Visual Neurosciences, MIT Press, 2003, pp. 215–233.
[33] M. Neuringer, W.E. Connor, C. Van Petten, L. Barstad, Dietary omega-3 fatty acid deficiency and visual loss in infant rhesus monkeys, J. Clin. Invest. 73 (1) (1984) 272–276.
[34] E.E. Birch, S.E. Carlson, D.R. Hoffman, K.M. Fitzgerald-Gustafson, V.L. Fu, J.R. Drover, Y.S. Castañeda, L. Minns, D.K. Wheaton, D. Mundy, J. Marunycz, D.A. Diersen-Schade, The DIAMOND (DHA Intake and Measurement of Neural Development) study: a double-masked, randomized controlled clinical trial of the maturation of infant visual acuity as a function of the dietary level of docosahexaenoic acid, Am. J. Clin. Nutr. 91 (4) (2010) 848–859.
[35] M. Razavy, Quantum Theory of Tunneling, World Scientific Publishing Co Pte Ltd., Singapore, 2002, July.
[36] G. Klimeck, M. McLennan, M. Lundstrom, G. Adams, NanoHUB.org—Online Simulation and More Materials for Semiconductors and Nanoelectronics in Education and Research, in: Proceedings of the 8th IEEE Conference on Nanotechnology, Nano, 2008, pp. 401–404.
[37] C. Angeli, On the nature of the $\pi \rightarrow \pi^*$ ionic excited states: the V state of ethene as a prototype, J. Comput. Chem. 30 (2009) 1319–1333.
[38] T. Kundu, B. Pradhan, B.P. Singh, Origin of methyl torsional potential barrier—an overview, Proc. Indian Acad. Sci. (Chem. Sci.) 114 (6) (2002) 623–638.
[39] A.E. Allen, M.A. Cameron, T.M. Brown, A.A. Vugler, R.J. Lucas, Visual responses in mice lacking critical components of all known retinal phototransduction cascades, PLoS One 5 (11) (2010) e15063.
[40] W. Overhauser, W. Albert, Polarization of nuclei in metals, Phys. Rev. 92 (2) (1953) 411–415.
[41] F.A.L. Anet, A.J.R. Bourn, Nuclear magnetic resonance spectral assignments from nuclear overhauser effects, J. Am. Chem. Soc. 87 (22) (1965) 5250–5251.

[3] Dr Jo Nurse, Division of Mental Health, Department of Health, UK 2007 £77 billion, 2010 £105 billion. Also Global Forum of Health.