Omega-3 PUFA profoundly affect neural, physiological, and behavioural competences – implications for systemic changes in trophic interactions

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Abstract

In recent decades, much conceptual thinking in trophic ecology has been guided by theories of nutrient limitation and the flow of elements, such as carbon and nitrogen, within and among ecosystems. More recently, ecologists have also turned their attention to examining the value of specific dietary nutrients, in particular polyunsaturated fatty acids (PUFA), among which the omega-3 PUFA, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) play a central role as essential components of neuronal cell membranes in many organisms. This review focuses on a new neuro-ecological approach stemming from the biochemical (mechanistic) and physiological (functional) role of DHA in neuronal cell membranes, in particular in conjunction with G-protein coupled receptors (GPCRs). We link the co-evolution of these neurological functions to metabolic dependency on dietary omega-3 PUFA. We outline ways in which deficiencies in dietary DHA supply may affect, cognition, vision, and behaviour, and ultimately, the biological fitness of consumers. We then review emerging evidence that changes in access to dietary omega-3 PUFA may ultimately have profound impacts on trophic interactions leading to potential changes in community structure and ecosystem functioning that, in turn, may affect the supply of DHA within and across ecosystems, including the supply for human consumption.

Key words: behaviour, biological membranes, DHA, ecological fitness, food-web ecology, G-protein coupled receptors, neurophysiology, omega-3 polyunsaturated fatty acids

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I. INTRODUCTION

Trophic ecology investigates patterns of dietary nutrient and energy flow from various sources to consumers (Hanley & La Pierre, 2015; Garvey & Whiles, 2016). These nutrient and energy flows are processed by the consumers’ metabolism and influence their fitness including somatic growth, reproduction, and survival (Orr, 2009). Therefore, to comprehend the functioning of nutrients and energy within a food web, one must combine diet metabolism and its functions within a consumer with ecological processes, such as predator–prey interactions. Yet, the literature dealing with effects of diet quality on the performance of individuals, e.g. their physiology, life history, and behaviour, is still somewhat separate from the literature on food-web ecology and trophic interactions among species. For example, the knowledge of how diet quality affects neural development of consumers can help us better understand the dynamics of how consumers detect their prey and how prey avoid being consumed. Furthermore, integrating answers to these questions with trophic ecology models will allow researchers to more realistically test the resilience of food webs to ongoing global change and to how such changes could affect nutrient supply to humans. The primary aim of this synthesis is to demonstrate that integration of existing literature from these different levels of biological complexity (i.e. from molecules to food webs) and thereby to provide valuable and novel perspectives on trophic ecology and generate new testable hypotheses of interest to ecologists and evolutionary biologists.

Measurements of macronutrients and trophic tracers (e.g. bulk stable isotope analysis of carbon and nitrogen) are common in trophic ecology, but do not provide sufficiently fine resolution to evaluate functional effects of diet on the physiology and behaviour of consumers (Müller-Navarra et al., 2000). A more functional approach involves the investigation of micronutrients, which are essential for normal physiological functioning of consumer tissues and cannot be synthesized de novo by the consumer, either in whole or in part. One group of essential micronutrients that must routinely be supplied to consumers are omega-3 polyunsaturated fatty acids (omega-3 PUFA), such as alpha-linolenic acid (ALA; 18:3ω3), eicosapentaenoic acid (EPA; 20:5ω3), or docosahexaenoic acid (DHA; 22:6ω3) (Carlson & Neuringer, 1999). Omega-3 PUFA can affect consumer growth and reproduction (Müller-Navarra et al., 2000; Copeman et al., 2002; Brett et al., 2009; Guo et al., 2016), health and physical condition (Arts & Kohler, 2009), and behaviour (Bell et al., 1995; Broadhurst et al., 2002; Benítez-Santana et al., 2014, 2007). Yet, most animals cannot de novo synthesize the parent fatty acid ALA, because they lack functional Δ15-desaturase, which is required to form the omega-3 ethylene bond. In addition, conversion of ALA to EPA and DHA is inefficient in many animals such that they benefit from obtaining EPA and DHA ‘preformed’ in their diet. Therefore, direct dietary uptake of omega-3 PUFA is required. Omega-3 PUFA are synthesized at the base of food webs by primary producers (e.g. algae, grasses) and are then selectively retained by consumers at higher levels in the food web. The unique position of omega-3 PUFA in food webs and their physiological importance, especially for neurological functions, should be promoted to researchers who study the effect of diet on the physiological and behavioural adaptations that consumers employ in trophic interactions to gain access to these essential micronutrients. This novel holistic approach has considerable potential to provide a deeper ecological understanding across all levels of biological complexity from biochemical processes within cells to individuals, populations, communities, and whole ecosystems.

We here mainly focus on the importance of DHA in the context of vertebrate consumers (Fig. 1), because of the extensive literature available on this topic. It should be noted that, in invertebrates, other omega-3 PUFA can have similar functions as DHA, however literature in this field is more scattered (see Section III.1). We summarize the importance of DHA for the formation and degradation of synapses and neurons, which is directly related to transmission activity via these neuronal junctions, by increasing the activity and thus signalling capabilities of neuronal membrane-bound receptors, required for vision, mood, memory and motor abilities and other cognitive traits. We then describe how the links between neuronal tissue function and cognitive skills likely interact to affect the fitness and trophic relationships of consumers, although this is currently understudied and investigations relating laboratory findings to natural ecosystems are scarce. Finally, we demonstrate how changes in net primary production of omega-3 PUFA caused by climate warming might influence the supply of these essential dietary micronutrients to consumers across all trophic levels, including humans.

II. THE CELLULAR FUNCTIONS OF OMEGA-3 PUFA

1. Composition and properties of omega-3 PUFA-containing membranes

Most aquatic and terrestrial organisms, from polar to tropical ecosystems, require omega-3 PUFA for their survival (Hixson et al., 2015; Colombo et al., 2016). The specific biochemical
The composition of cell membranes varies significantly among organelles, tissues, and organisms, and can contain up to 1500 different lipid species and several hundred transmembrane proteins that are in a state of rapid flux (Wassall & Stillwell, 2009). Apart from sterols, all membrane lipids contain three specific features: a hydrophilic polar head group, a central group (glycerol or sphingosine) and hydrophobic long hydrocarbon chains. In animals, the vast majority of polar head groups contain phosphate [e.g. phosphatidylcholine, (PC); phosphatidylyserine (PS); phosphatidylethanolamine (PE); phosphatidylinositol (PI)] (Antonny et al., 2015; Kalisch, Dörmann & Holz, 2016). The state of the lipid phase they form depends on the geometry of the involved polar lipids. Molecular species with small polar head groups such as PE and PS, and long PUFA induce negative curvature stress and form hexagonal II (HII) or cubic phases, whereas species with large polar headgroups and short saturated fatty acids form hexagonal I (HI) phases and induce the formation of small-curvature lipids (e.g. PC, PI); together these form the lamellar lipid phases found in most biological systems (Fig. 2) (Jouhet, 2013).

Transmembrane proteins are embedded in the lipid matrix, where, if not anchored to the cytoskeleton or the extracellular matrix, they are able to move freely in the lamellar lipid phases, also referred to as liquid crystalline or bilayer. In vitro, and in some biological membranes such as the myelin sheath, lipids also form non-liquid, non-bilayer solid phases, especially at low temperatures and if they...
contain long saturated fatty acids (Ruocco & Shipley, 1984; Mason, 1998). Alterations in hydration rate, pH, the concentration of cations and temperature may alter lipid organization and induce phase transitions (Ding et al., 2005). Therefore, in biological membranes, the composition of different polar lipids must be constantly adjusted to maintain a fully functioning lipid bilayer, while still matching local requirements of proteins for negative or positive curvature stress. This can lead to significant changes in membrane lipid composition, especially in poikilothermic species experiencing changes in temperature across the different seasons (Käkelä et al., 2008). Highly curved membranes such as the endoplasmatic reticulum, the inner mitochondrial membrane, or the rod outer disk membrane of the retina, require enrichment of HII-forming lipids to reduce negative curvature stress (Murphy, 1982; van Venetië & Verkleij, 1982; Vögler et al., 2004; Griffith, 2010). For example, mitochondria require diphosphatidylglycerol (DPG, cardiolipin) to maintain lamellar phases at low pH, while also maintaining the high negative curvature of their inner membrane in the cristae, which would otherwise induce HII transition in charged phospholipid systems such as PS (Sedelon, Kaye & Marsh, 1983; Sedelon, 1990). The broad spectrum of biochemical processes in which polar lipids are directly involved and the need to buffer changes in physicochemical properties explains the necessity for the great diversity of lipid species (Dowhan, 1997) that contribute to the survival of organisms under various environmental conditions.

The phase of membranes is determined by the polar head group and also by the acyl side chains. In this context, DHA is conspicuous among all fatty acids. In vertebrates, it is enriched in the membranes of neurons (Breckenridge, Gombos & Morgan, 1972) and sperm (Neill & Masters, 1972) and even exceeds 50 mol% of all fatty acids of the retinal rod outer segment (Wiegand & Anderson, 1983), where a high amount of dipolyunsaturated phospholipids have also been identified (Miljanich et al., 1979). DHA preferentially accumulates in the PE- and PS-rich inner (cytoplasmic) leaflet and to a lesser extent in PC (Emmelot & Van Hoeven, 1975; Knapp, Hulin & Salem, 1994). The key feature of DHA is its repeating =C–C= unit, which reduces the energy barrier for rotation about the C–C bonds, so that conformation changes within the molecule occur very rapidly, i.e. within a few nanoseconds at C2 to less than 100 ps near the terminal methyl group (Gawrisch & Soubias, 2000). The particular importance of this high number of double bonds within the aliphatic chain can be seen by solid-phase nuclear magnetic resonance (NMR) comparing DHA to omega-6 docosapentaenoic acid (DPA, 22:5ω6). The loss of the omega-3 double bond dramatically reduces the flexibility at the methyl end due to increased van-der-Waals interaction with saturated fatty acids. As a result, the DHA alkyl chain has a higher density near the lipid–water interface, disrupts the order within the bilayer, especially that of adjacent saturated fatty acids (Saiz & Klein, 2001; Feller, Gawrisch & MacKerell, 2002; Eldho et al., 2003; Soubias & Gawrisch, 2007) and is more twisted...
and less bent than other fatty acids (Broadhurst et al., 2016).

Thus, in general, DHA-containing phospholipids have a tendency to form non-lamellar phases with surrounding lipids (Shaikh et al., 2001) and can increase negative curvature strain on adjacent proteins (Epand, 1998). PC containing one DHA cover, on average, 11–13% more area of the membrane than PC containing only fatty acids with <2 double bonds (Koenig, Strey & Gawrisch, 1997; Smaby et al., 1997; Eldho et al., 2003), while forming thinner membranes (Dratz et al., 1985). In summary, membranes containing high amounts of DHA are compressible, very permeable and support high rates of lipid flip-flop (Stillwell & Wassall, 2003), all of which support dynamic cell membranes that have to undergo constant changes for normal functioning.

Depending on the phospholipid species, PUFA, typically esterified at the sn-2 position in phospholipids, have substantial effects on interactions within the membrane bilayer, especially in combination with cholesterol. Cholesterol, with its rigid tetra cyclic ring structure and single hydroxyl group, has a very different behaviour biochemically compared to DHA and can account for as much as 50% of total lipid content in membranes (Silvius, 2003). Cholesterol is soluble in PE(16:0/18:1) and PC(16:0/18:1) at ~51 mol% and 65 mol% respectively, while its solubility is reduced to 31 mol% in PE(16:0/22:6) and 55 mol% PC(18:0/22:6) and drops further to 8.5 mol% and 11 mol% in PE(d22:6) and PC(d22:6) (Shaikh et al., 2006). The different solubilities of cholesterol in phospholipids with variably saturated acyl side chains result in polar lipids not being evenly distributed within a cholesterol-containing membrane bilayer. Instead, molecular lipid species accumulate in patches of specific composition, that together with the residing proteins, form local domains (Lungwood & Simons, 2010). For example, lipid rafts are highly ordered domains, enriched in saturated sphingolipids and cholesterol, which are insoluble in cold non-ionic detergents and often harbour signalling proteins, especially kinases (Brown & London, 2000; Pike, 2006). In the presence of cholesterol in the lipid bilayer, phospholipids containing DHA will assemble into highly dynamic lipid non-raff domains of low order and are particularly enriched in the innermost two annular layers of rapid signalling transmembrane proteins, such as ion channels or G-protein coupled receptors (GPCR) (Polozova & Litman, 2000; Brazustowicz et al., 2002; Woods, Sharp & Brannigan, 2019). While in general EPA shares similar domain-forming properties, the distribution of DHA and EPA between raft and non-raft domains differs slightly (Williams et al., 2012). It can thus be speculated that this contributes to some of the differences regarding the physiological properties and the ability to enhance receptor activity between the individual omega-3 PUFA species, leading to the unique importance of DHA for cognitive abilities of consumers.

(2) Interaction of DHA with transmembrane receptors

The close association of omega-3 PUFA with GPCR in general is important for accelerated stimulus transmission in neural tissues, which helps optimize consumer fitness. Vertebrates express more than 800 GPCR, which display a highly conserved architecture consisting of seven transmembrane helices and are grouped into five classes, A-rhodopsin, B-secretin, C-glutamate, F-frizzled and the adhesion family, with class-A representing > 83% of the receptor family (Lagerström & Schiöth, 2008; Rosenbaum, Rasmussen & Kobilka, 2009). Their general structure consists of three extracellular loops (ECL1–3) and three intracellular loops (ICL1–3), the structural core built by the seven transmembrane helices (TM1–7) and an intracellular amphipathic helix (H8) (Gimpl, 2016). Activation of GPCR involves ligand binding to a pocket of the receptor, in most cases formed by ECL1–3, which stabilizes an active receptor conformation, followed by GDP dissociation from the Gα subunit of the G-protein and its exchange for GTP and finally dissociation of the G-protein-heterotrimer into Gα-GTP and the membrane-anchored subunits Gβγ, which eventually trigger the signalling cascade that induces an action potential (Nygaa et al., 2013). Many GPCR form homo- or hetero-dimers, or larger oligomers, however the physiological function of receptor self-association is controversial, and might involve another level of regulation of receptor activation (Gurevich & Gurevich, 2008; Dell’Orco, 2013; Gunkel et al., 2013; Durdagi et al., 2019).

The best investigated GPCR is the photoreceptor rhodopsin, which is the most abundant protein of the rod outer segment (ROS), is very densely packed within specialized disc membranes, and is responsible for monochromatic vision in the dark (Fig. 3A) (Palczewski, 2006). The ligand, the light-capturing chromophore 11-cis retinal, is covalently bound to TM7 via Schiff base and upon absorption of a photon is isomerized to an all-trans retinal configuration (Kiser, Golczak & Palczewski, 2014). This leads, through rapid (i.e. a few microseconds) conformation changes near the retinal binding pocket, to a transition to the inactive metarhodopsin I (MI) (Scherder, 2005). Binding of the G-protein transducer (G), and triggering of the signalling cascade is only enabled after transition to the active metarhodopsin II (MII) on timescale of milliseconds. This involves large-scale conformational changes, most notably, an outward tilt of TM5 and TM6 (Altenbach et al., 2008), and a reorganization of water-mediated hydrogen-bond networks within the protein that then presents an energetic barrier for receptor activation (Fig. 3B,C) (Grossfield et al., 2008; Standfuss et al., 2011). All-trans retinal molecules are then cleaved off the receptor, recycled, and a new 11-cis retinal molecule is joined with opsin to return to the inactive rhodopsin dark state, completing the visual cycle (Parker & Crouch, 2010).

The crucial part of receptor activation is the MI to MII transition, which leads to an overall stretching of the receptor, exposing hydrophobic residues to the water surface, introducing a hydrophobic mismatch and affecting the order of the surrounding membrane (Fig. 3C) (Salas-Estrada et al., 2018). It is thus of little surprise that the annular lipid composition has significant effects on the equilibrium and kinetics of receptor activation. As mentioned above, ROS...
Disc membranes have a particularly high proportion of DHA in phospholipids, which can even be esterified to both the sn-1 and sn-2 positions in PS and PE (Albert, Young & Paw, 1998). While the cholesterol content is very high in newly formed disc membranes, it decreases as they mature (Boesze-Battaglia, Hennessey & Albert, 1989). The high DHA content favours transition to the MII state and ultimately accelerates receptor activation and efficiency of signal transduction, requiring less photons for its activation and thus enabling, for example, vision at lower light levels (Soubias et al., 2015). Molecule dynamic simulations and saturation-transfer NMR experiments suggest ligand-like

![Figure 3](image)

**Fig 3.** (A) Scheme of rod cells and crystal structure of rhodopsin (PDB 1L9H): blue, TM1; cyan, TM2; green, TM3; lime, TM4; yellow, TM5; orange, TM6; light-red, TM7; dark-red, H8. Rhodopsin is very densely packed in the disc membranes of the outer segment, with on average only 1–2 protein diameters space between each molecule. This explains the high amount of docosahexaenoic acid (DHA) required for these specialized membranes, to prevent unspecific oligomerization and accelerate signalling. (B,C) Model of receptor activation. TM3 has a substantial influence on receptor stability in both the active and inactive state. The distance between TM3 and TM6 increases from 0.8 nm to about 1.5 nm in the active state (Neale et al., 2015). Excitation of dark-state rhodopsin leads to isomerization of retinal and initiates internal conformation changes (MI) ultimately resulting in global transition to the active MII state, which is characterized by an outward tilt of TM5 and TM6 and elongation of the protein. This increased exposure of hydrophobic residues (dark grey) by the protein induces negative curvature stress in the phospholipid bilayer, which can be compensated by polyunsaturated side chains in combination with polar phospholipid species, that tendentially favour negatively curved structures, such as phosphatidylethanolamine (PE) and phosphatidylycerine (PS), thus reducing the energy required for the transition from MI to MII. It is likely that the signal-transduction-enhancing properties of DHA are similar with regards to other G-coupled receptors found in the neuronal membrane such as serotonin or dopamine receptors, where the ligand binds to the extracellular domain of the receptor.
behaviour, equal to 16 binding sites per receptor, associated especially with TM5 and TM6, which undergo the greatest conformational changes, while TM1 and TM2 do not perform any major movement and have the weakest association with DHA (Soubias, Teague & Gawrisch, 2006; Venkatarkrishnan et al., 2013; Salas-Estrada et al., 2018). Interaction of DHA with the receptor most likely occurs via semi-aromatic π-stacking between the double bonds of the PUFA and aromatic side chains of the phenylalanine residues of the TMs (Grossfeld, Feller & Pitman, 2006; Soubias & Gawrisch, 2012; Molčanov & Kojić-Prodić, 2019). These interactions may facilitate solvation of GPCR in the non-raft domains of the cellular membrane, and combined with the flexibility of DHA compensate for hydrophobic mismatch during activation cycles (Huber et al., 2002). Additionally, PE head groups exhibit long-term interactions via hydrogen bonds with ICL3 especially in the inactive protein states, which might introduce negative curvature elastic stress in the membrane and additionally favours the transition to the active MII state of the receptor (Fig. 3C) (Salas-Estrada et al., 2018). Thus, the specific annular lipid composition, in particular high amounts of DHA, acts as catalyst, reducing the energetic barrier for the required structural changes during receptor activation and increases its kinetics, while reducing the required quantity of stimuli (e.g. photons) to trigger this process and increasing the efficiency of the receptor. Possible consequences for consumers include, for example, a direct correlation between dietary DHA and hunting success in low-light conditions (Bell et al., 1995; Navarro et al., 1997).

Besides rhodopsins, class A of GPCR contains a huge variety of receptors important for immune signalling, regulation of hormone release, blood pressure and coagulation, but those closest related to rhodopsin are expressed in neuronal structures and include α- and β-adrenergic, dopamine, histamine, adenosine, muscarinic acetylcholine, opioid and 5-hydroxytryptamine (5-HT, serotonin) receptors (Jacobson & Costanzi, 2012; Venkatarkrishnan et al., 2016). Similar to rhodopsin, it has been shown that DHA interacts directly with those receptors and is probably also involved in resolving hydrophobic mismatch and providing non-raft domains for optimized receptor oligomerization, in order to enhance signalling capabilities by acceleration of conformation change kinetics (Guixà-González et al., 2016). As key elements of neuronal synapses, the smallest unit of neuro- logical structures and a central element for neuronal tissue function (Südhof, 2018), their signal efficiency determines the power of sensory, motor and cognitive capabilities of a species (Abraham, Jones & Glanzman, 2019). For example, dopamine receptors (D1–5) are abundant in brain regions associated with motivation, pleasure, cognition, memory, and fine motor control and have been shown to form numerous heterodimers with other dopamine and non-dopamine receptors, whose biological role has only partly been resolved (Beaulieu, Espinoza & Gainetdinov, 2015). Serotonin receptors (5-HT1,2,4–7) with the exception of HT1, which is an ion channel and responsible for nausea and emesis, modulate the release of many other neurotransmitters and hormones and are involved in neurological processes such as aggression, anxiety, appetite, cognition, memory, mood, sleep and thermoregulation (Carhart-Harris & Nutt, 2017). Numerous drugs used in psychiatric and neurological diseases specifically bind to these receptors and alter their function and their treatment success might be linked with brain DHA levels. It should be emphasized that signalling activity or inactivity of those receptors significantly contributes to the formation or degradation of the synapses, which are degraded by low activity levels. This provides a possible direct linkage between the activity modulating DHA and the development of neuronal structures and cognitive abilities including memory, as well as visual acuity (Sheehan et al., 2016; Cohen & Ziv, 2017).

Although a central focus of this synthesis is on the interaction between DHA and GPCR, it should be stressed that DHA is also essential for other biochemical processes. For example, oligomerization behaviour, and thus also activity of nicotinic acetylcholine receptors (an ion channel found at the neuromuscular junction and responsible for rapid muscle movement) is also dependent on lipid non-rafts formed by DHA or EPA in the neuronal membrane and also accumulates PUFA-containing phospholipids in its inner annular layers (Woods, Sharp & Brannigan, 2019). Lipid non-rafts also increase membrane translocation of protein kinase B, increasing its activation and thus also expression of genes important for cell survival and reproduction (Slater et al., 1994; Akbar et al., 2005). Furthermore, a correlation between DHA content of membranes and molecular activity of the Na+K+-ATPase has been reported (Turner, Else & Hulbert, 2003), which affects local metabolic rate. In this case DHA might also be involved in the regulation of oxidative stress, as the high number of double bonds can act as a buffer for reactive oxygen species generated by high cellular respiration rates (Brenna & Diau, 2007) and, in this context, the role for omega-3 PUFA in increasing mitochondrial efficiency has been discussed (Sullivan et al., 2018). In combination with the conversion to the anti-inflammatory mediators maresins, protectins and resolvins by lipoxygenases, DHA, but also EPA, has an indirect protective effect on neuronal structures by restraining inflammatory reactions in the close vicinity of these fragile, but highly active tissues and can thus prevent neurodegeneration (Dyall, 2015; Serhan et al., 2015; Duvall & Levy, 2016; Bhatt et al., 2019; Preston Mason, 2019). Another important consideration is that axons do not contain ribosomes or endoplasmic reticulum, so that the entire protein synthesis of neurons, including their receptors, takes place in the vicinity of the nucleus, following passive transport distally. An increased membrane fluidity by the lipid non-rafts could enable faster transport via the neuronal membrane, which, in turn, would benefit accelerated synapse formation (Südhof, 2018). The flexibility and high fluidity promoted by DHA can also enhance the kinetics for the formation of synaptic vesicles, which deliver neurotransmitters to the synaptic cleft in response to action potentials. This might also contribute to faster neuronal signalling (Antonny et al., 2015; Lauwers, Goodchild & Verstreken, 2016).
In summary, DHA is a unique fatty acid that, due to its high flexibility, can alter local membrane properties without disrupting the phospholipid bilayer. Esterified to phospholipids with small polar headgroups such as PE and PS, it induces negative curvature stress, which, together with its ability to compensate for hydrophobic mismatch, can significantly alter the activity of signalling transmembrane receptors that have to undergo rapid conformation changes, and/or require specific lipid non-raft environments for proper oligomerization. This will, consequently, have implications at larger scales, as altered (i.e. decelerated) signalling capabilities directly affect the interaction of cells, thus tissue efficiency. Metaphorically, DHA is like the lubricant of an engine, reducing the friction of cylinder movement and indirectly contributing to increased power output and enhanced performance. As will be discussed in the next sections, the greatest effect of DHA deficiency can be linked to receptors found in neuronal structures, such as the eye (rhodopsin) or the cerebral cortex and the cerebellum (serotonin and dopamine receptors), which are responsible for visual acuity or cognition, memory and behaviour, respectively. This provides a direct link between DHA and sensory and cognitive abilities.

III. THE ROLE OF OMEGA-3 PUFA AT THE INDIVIDUAL LEVEL

(1) The importance of omega-3 PUFA for different species

In this section we review studies dealing with the species-specific importance of omega-3 PUFA that ultimately result in a better understanding of their importance for neurological structures in general. Although the best-studied functional linkage, across all species, centres around the effect on light-sensing capabilities by rhodopsin, similar patterns are elucidated in the literature for other GPCR, which can be found in species from all kingdoms (Ernst et al., 2014). However, their interaction with DHA, EPA, or ALA in invertebrates is far from clear. For example, the majority of terrestrial invertebrates do not contain EPA or DHA (Stanley-Samuelson et al., 1988; Buckner & Hagen, 2003; Wang et al., 2006; Rumpold & Schlüter, 2013), while most aquatic/amphibiotic insects are rich in EPA, but have considerably less DHA (Borisova et al., 2016; Sushchik et al., 2017, 2013), which also reflects the composition of the phospholipid membranes in their neurological structures (Ziegler et al., 2013; Sushchik et al., 2017). Even if fed in excess, DHA is eventually broken down to fatty acids ≤20 carbons long in most terrestrial invertebrates (Stark et al., 1993; Shen et al., 2010; Vrablik & Watts, 2013).

Visual signal transduction in invertebrates has been best scrutinized in *Drosophila melanogaster*, which, like other insects, possess a compound eye comprised of reiterating hexagon-shaped ommatidia containing 20 cells with eight photoreceptors each (Montell, 2012). The main rhodopsin in flies (Rh1) resembles melanopsin in humans, which is activated by blue light and found in intrinsically photosensitive retinal ganglion cells. In humans, it is responsible for light/dark adaptation via iris contraction and directing the circadian rhythm, however, it only contributes <1% of total rhodopsin (Nasir-Ahmad et al., 2019). Interestingly, and, in contrast to other rhodopsins, drosophila Rh1 and human melanopsin are bistable and lack a visual cycle, but instead use a second photon to convert all-trans retinal back to 11-cis-retinal, suggesting that both share a common ancestral gene (Parker & Crouch, 2010). Sequential and structural conservation of the receptor suggests that there is no direct genetic connection to differences in membrane composition among species that share similar signalling receptors. We speculate that ALA/EPA-based systems render the GPCR required for vision and cognition less efficient but still functional, whereas DHA-based systems are associated with enhanced visual acuity and cognition. It should also be noted that partial degradation of DHA to EPA or ALA provides raw energy, which, for some species, might be of higher value than increased neurological traits. Unfortunately, data comparing the activity of invertebrate rhodopsin or other GPCR in presence of either ALA, EPA or DHA are not available, therefore this hypothesis cannot currently be rigorously assessed from a biochemical perspective. Some invertebrates obtain EPA from their gut microflora (Sampedro, Jeannotte & Whalen, 2006), and for *Caenorhabditis elegans* capabilities of *de novo* synthesis of EPA have been reported (Menzel et al., 2019). Recently, it has been discovered, that genes for *de novo* biosynthesis of PUFA are widespread in invertebrates, including proof of their theoretical function, however, if and under which circumstances they are expressed, or whether they are just an inactive evolutionary artefact has not been clarified (Kabeya et al., 2018).

In vertebrates, conversion of ALA to tetracosahexaenoic acid (24:6ω3) is performed in the endoplasmatic reticulum, mainly by hepatocytes, by a series of desaturases and elongases. The latter metabolite is then transferred to the peroxisomes for a single cycle of β-oxidation to obtain DHA (Voss et al., 1991). In species expressing Δ4-desaturase, which has not yet been definitively clarified for humans (Martinez et al., 2010), DHA can also be directly synthesized from omega-3 docosapentaenoic acid (DPAω3) (Voss et al., 1991). Except for the liver, endogenous synthesis of DHA in the brain and other tissues is low, and thus levels of DHA in the body are maintained primarily by uptake from dietary or liver sources (Ouellet et al., 2009). Although mammals are generally able to convert, at various efficiencies, ALA to DHA and other long-chain PUFA (LC-PUFA), especially during pregnancy, conversion efficiency varies among species and seems to be limited for most non-herbivores, including humans (James, Ursin & Cleland, 2003; Burdge & Calder, 2006). Nevertheless, DHA is important for neurochemistry in all vertebrates, as they share quite conservative signal transduction mechanisms. As an example, the distribution of central nervous receptors of fish resembles humans, so that, despite significant differences in neuroanatomy,
particularly in the prefrontal cortex, and being poikilothermic, fish are used as model organisms to study neurological diseases, or the effects of malnutrition on the development of neurological structures (Vargas, López & Portavella, 2009; Panula et al., 2010; Mueller, 2012). Further assumptions regarding the importance of DHA and tightly entangled GPCR for the development of cognition can be made when comparing the genome of chimpanzees to humans (International Human Genome Sequencing Consortium, 2001; The Chimpanzee Sequencing and Analysis Consortium, 2005). The majority of variation has been identified in genes responsible for immune signalling, but a significant amount is also linked with brain development and neurological functions (Cheng et al., 2005). The best investigated example is FOXP2, which is a highly conserved transcription factor, that has been linked with impairments in speech and language development and its human variant is associated with an increased development of the cortico-basal ganglia circuits (Lai et al., 2001; Enard et al., 2009), specifically those structures that were degraded in dietary omega-3 PUFA deprived rats (Ahmad et al., 2008; Davis et al., 2010). Most notably, expression of the human isoform leads to increased dopamine signalling, striatal synaptic plasticity and dendrite morphology and seems to significantly improve learning capabilities in rodent models (Enard et al., 2009; Schreiweis et al., 2014). Other genes that show significant variations are SRGAP2, ARHGAP11B, BOLA2, DUF1229, and various non-coding regulatory regions, all affecting brain architecture, synapse maturation, number of synapses, synaptic density and synaptic plasticity (Sassa, 2013; Sousa et al., 2017), and are closely related to signal transduction efficiency and signal-processing capacities via GPCR.

A centralized nervous system has arisen independently several times during evolution, and although it would be interesting to compare the neurochemistry of, e.g. cephalopods, which possess a highly developed brain and have access to a diet enriched in LC-PUFA, to vertebrates, such data are, unfortunately, currently not available (Shigeno et al., 2018; Schnell et al., 2021). Cetaceans also possess a high number of neurons in the cerebral cortex compared to total brain mass (Montgomery et al., 2013; Sousa et al., 2017), which they probably require for their extensive social behaviours (Dunbar, 1992; Sawaguchi, 1992), physiological adaption to their environment (Shultz & Dunbar, 2006; Mace, Harvey & Clutton-Brock, 2009) and sensory specializations (Barton, Purvis & Harvey, 1995; Marino et al., 2007; Huggenberger, 2008), but data regarding DHA content in this brain region are scarce. Herbivorous terrestrial vertebrates, which require efficient neurological signalling, e.g. for evasion of predators or social interactions, lack dietary DHA and must compensate through the conversion of ALA to DHA (Geiser et al., 2007; Wood et al., 2008; Kouba & Mourot, 2011). High conversion rates have also been observed in birds (Infante, Kirwan & Brenna, 2001; Klaiman, Price & Guglielmo, 2009) and snakes, which possess specialized high-frequency contraction muscles that require rapid signalling (Infante, Kirwan & Brenna, 2001).

While it is frequently stated that many animals need dietary LC-PUFA the full scope of this ’need’ (including establishing critical thresholds) is not well defined. Further, while a dietary requirement for LC-PUFA is known to exist for humans, when considering other species’ ecological strategies, both their diet and their requirement for cognition and neuronal signalling has yet to be taken into account. The costs of providing DHA for tissue growth must be compensated by a significant benefit, such as higher cognitive performance, that also fits within that species’ overall ecological strategy. Further research is therefore required to understand the flux of micronutrients, such as DHA, in and across ecosystems and the requirements of their inhabitants to understand, and eventually predict, the impact of changes in net DHA production on ecosystems (Závorka et al., 2019).

(2) Importance of omega-3 PUFA for tissue function and for behaviour in animals

Neural tissues in aquatic and terrestrial animals are rich in omega-3 PUFA, in the case of vertebrates particularly DHA (Broadhurst et al., 2002; Ebm et al., 2021). The close linkage between omega-3 PUFA and activity of GPCR renders omega-3 PUFA essential for the proper functioning of neuronal tissue. Although several biochemical functions described above are specific for DHA, several studies that link omega-3 PUFA deficiency with tissue function show similar effects even for species that do not contain DHA, but instead utilize EPA and/or ALA. This indicates that all omega-3 PUFA are able to enhance GPCR signalling, but to different extents (DHA> EPA>ALA). However, since most studies have been performed in vertebrates, we focus on DHA in conjunction with rhodopsin (i.e. central to visual acuity) and dopamine and serotonin receptors (central to cognitive functions including learning and memory, mood and behaviour as well as motor abilities). Studies with invertebrates mainly have been performed in D. melanogaster, a species lacking fatty acids \(18:3\) (Ziegler et al., 2015). Adaption to poor food quality by reducing learning abilities and adult size led to faster development and increased reproduction of D. melanogaster (Kols & Kawecki, 2008). In Daphnia sp., somatic growth, reproduction and behaviour, including evas-ion of predators, could be linked to serotoninergic signalling and might thus also be affected by the availability of dietary omega-3 PUFA (Campos et al., 2019, 2013).

For fish, dietary DHA has been associated with visual acuity, hearing, and schooling behaviour (Masuda et al., 1998; Ishizaki et al., 2001). Atlantic herring (Clupea harengus) reared on diet containing no DHA were less-effective predators,
especially at low light intensity and reduction of brain DHA levels were compensated by an increase in EPA and DPAω6 (Bell et al., 1995). In another study, DHA deficiency led to reduced escape behaviour in response to sound, which was correlated with altered signalling via muscarinic acetylcholine receptors in Mauthner cells (Benítez-Santana et al., 2014). Some fish (e.g. common carp Cyprinus carpio) perform specific avoidance behaviours, stirring up a cloud of fine sediment which allows them to hide upon exposure to olfactory cues released from injured skin of conspecifics; this behaviour depends on serotoninergic activity within the brainstem (Hoglund et al., 2005). Dietary omega-3 LC-PUFA deficiency in Daphnia sp. also might lead to decreased serotonin signalling and ultimately to changes in their avoidance behaviour to fish, rendering them more exposed to predation, or leading to other maladaptive life-history strategies (McCoole et al., 2012; Campos et al., 2013, 2019). Furthermore, it was shown that dietary DHA and/or the ability to synthesize DHA from other PUFA is crucial for the colonization of freshwater by sticklebacks (Gas-trodnus sp.) (Ishikawa et al., 2019). Although shown for only a small number of species, it seems that freshwater fish may be better at converting ALA to DHA, but conversion of EPA to DHA has been shown to be more effective and contributes 10 times more to the building of neuronal structures than the less-efficient conversion of ALA to DHA (Moure et al., 1996; Mourente & Tocher, 1998). Dietary deficiency of DHA has also been shown to have irreversible transgenerational effects, as offspring of female red drum Sciaenops ocellatus raised on a DHA-deficient diet displayed poor antipredator escape behaviour and low visual stimuli responsiveness, which was not improved by subsequently supplying a DHA-enriched diet (Fuiman & Ojianguren, 2011; Hou & Fuiman, 2020).

Several studies in rats, raised under extreme omega-3 PUFA deprivation over multiple generations, demonstrate that DHA is continuously replaced by DPAω6 under conditions of malnutrition, however, the extent differs among tissues and even amongst individual areas of the brain (Bourre et al., 1989; Carrié et al., 2000; Salem et al., 2001; Murthy et al., 2002; Able et al., 2014; Cardoso et al., 2014). The consequences of malnutrition were clearly observed in the retina, as highlighted by a reduction in the amplitude of electroretinograms indicating impaired visual acuity. Individuals also required more repetitive training, which indicates learning impairment (Bourre et al., 1989). The latter is probably caused by degradation of dopaminergic neurons in the substantia nigra pars compacta and ventral tegmental area as result of reduced receptor activity (Ahmad et al., 2008).

Dietary omega-3 PUFA deficiency also led to a decreased density of ventral striatal dopamine D2-like receptors and a higher density of dopamine D1-like receptors in the caudate nucleus, similar to several rodent models of depression used in clinical studies (Davis et al., 2010). Furthermore, effects of DHA deficiency could be directly linked to serotonin signalling, as it led to increased climbing behaviour during the forced swim test, in combination with fluoxetine administration, a selective serotonin reuptake inhibitor which is prescribed for depression (Able et al., 2014). In addition, a decreased dietary omega-3/omega-6 PUFA ratio induced autistic-like behaviour in mice (Weiser et al., 2016). Furthermore, altered activity levels of several other key brain enzymes, including decreased Na+/K+-ATPase activity in the synaptosomes, was reported (Bourre et al., 1989). In omega-3 PUFA deficiency experiments, recovery to normal levels by DHA supplementation required 2–3 weeks for brain and retina, while normal levels were achieved within 3–4 days in liver (Contreras et al., 2008). Some functions, such as spatial and memory task acquisition, could be restored (Moriguchi & Salem, 2003), however, electroretinographic changes persisted, indicating persisting decreased visual acuity (Connor & Neuringer, 1988; Weisinger et al., 2001). Similar cognitive and visual deficiencies were observed in a Mfsd2a−/− mice exhibit severe deficiencies in brain DHA, despite normal liver values, microcephaly and an increase in brain omega-6 PUFA levels and suffer from impaired spatial orientation and memory defects, had reduced preferences for novel objects, were significantly more anxious and showed decreased activity during open field tests (Lim, Hoshiba & Salem, 2005; Nguyen et al., 2014; Wong et al., 2016). In supplementation studies, DHA enhanced spatial orientation due to increased neurogenesis in the hippocampus (He et al., 2009) and memory-related learning abilities in rodents (Hashimoto et al., 2015), although the latter study focused on inflammatory processes within the brain as the cause, rather than effects of DHA on brain signaling. Brain DHA levels could not be further increased if rats obtained more than 0.4% of their energy from omega-3 PUFA, irrespective of the omega-6 PUFA content of their diet (Bourre et al., 1989). Finally, in a rat neuronal cell culture model, DHA nanoliposomes enhanced axonal growth, dendrite formation and synaptogenesis, indicating faster and more efficient formation of neuronal structures under DHA supplementation (Malaplate et al., 2019). These studies provide repeated evidence that dietary omega-3 PUFA, in particular DHA, are key for normal behaviour of aquatic and terrestrial consumers.

In humans, DHA deficiency has, increasingly, been linked to Parkinson’s disease (Sanadi et al., 2006; Fabelo et al., 2011), depression (Lin, Huang & Su, 2010; McNamara, 2010; Tatebayashi et al., 2012), autism (Brown & Austin, 2011) and Alzheimer’s disease (Conquer et al., 2000; Schaefer et al., 2006; Féart et al., 2008; Samieri et al., 2012), i.e. diseases that are also linked to altered dopamine and serotonin signalling. Increased brain DPAω6 levels have been identified in some of these studies. A possible mechanism could be that, due to a reduction of dopamine and serotonin receptor activity, synapses are prone to degradation since their formation and maintenance is strongly dependent on signalling activity (Zuo et al., 2013; Sheehan et al., 2016; Cohen & Ziv, 2017). There are multiple reports of PUFA supplementation significantly augmenting the antidepressant effects of selective serotonin reuptake inhibitors (Jazayeri et al., 2008; Laino et al., 2010; Gertsik et al., 2012), probably due to increased signal efficiency and transduction via 5-HT receptors.
All these studies indicate that DHA deficiency leads to impairments in vision, cognition, motor and sensory capabilities, as well as mood changes, and altered behaviour (i.e. reduced activity, boldness, and exploration) by affecting neurological structures rich in the closely related receptors, rhodopsin, dopamine and serotonin. The provision of essential omega-3 PUFA to the next generation (e.g. by enrichment in eggs, during pregnancy or via breastfeeding) significantly benefits the cognitive capabilities of the offspring, including humans (Salem et al., 2001). Signalling via other receptors such as adrenergic, or acetylcholine receptors could also be impaired, however, the effect might be less prominent in the study subjects. It has to be mentioned, however, that these studies have several limitations. Most studies in humans investigating a link between neurological diseases and omega-3 PUFA use blood components, that, although showing strong correlations with peripheral tissues, may not precisely reflect the composition of the central nervous system and there may also be differences regarding the metabolism and incorporation of omega-3 PUFA (Brown, Pang & Roberts, 1991; Tu et al., 2013; Arellanes et al., 2020). Furthermore, the methods used to evaluate behavioural changes in rodents, such as the forced swim test or the Morris water maze test are somewhat controversial and thus their ultimate value for assessing depression or other psychiatric diseases is unclear (Reardon, 2019), despite being valuable for assessing spatial orientation competency. Finally, there are few, if any, studies that extrapolate these laboratory findings to effects on individuals in their natural habitat, thus there is scant information available that would allow us to translate biochemical and medical findings into the context of animal ecology (Niemelä & Dingemanse, 2014). Changes in cognitive skills and ecologically important behavioural traits reported in the above-mentioned laboratory studies might have effects on performance and, ultimately, fitness if they occur in wild animal populations. For example, in a study on the mouse lemur (Microcebus murinus), individuals with lower performance in problem solving displayed a reduced body mass index (BMI) over the winter season (Huebner, Fichtel & Kappeler, 2018). Yet, due to the lack of ecological studies, it remains unclear which of the many-fold effects of dietary omega-3 PUFA will be crucial for fitness of consumers in the wild. While we focus our review mainly on the neurobiological importance of DHA, it should be noted that the trajectory of dietary impacts of omega-3 PUFA on consumer fitness might be context dependent and carefully designed field experiments will be needed to disentangle them.

IV. TROPHIC TRANSFER OF LC-PUFA IN ECOSYSTEMS AND THEIR PROVISION TO HUMANS

(1) Producers of omega-3 PUFA in ecosystems

Plants, algae, fungi and some bacteria and animals possess the Δ15-desaturases required to synthesize the omega-3 double bond in PUFA (Sperling et al., 2003; Yoshida et al., 2016; Kabeya et al., 2018; Allemann, Shulse & Allen, 2019; Babaran et al., 2020), which they use to adjust their cell membranes to temperature changes (Higashi et al., 2015), or to produce oxylipins, which comprise both inter- and intraspecies signalling molecules analogous to products of cyclooxygenases in animals (Rettner et al., 2018; Deboever et al., 2020), or defensive agents against bacteria and herbivorous grazers (Lauritano et al., 2016; Meyer et al., 2018). In algae, DHA might also be linked to GPCR function, in particular that of rhodopsins, and could increase the efficiency of phototaxis, a process unknown in prokaryotes, that has evolved independently at least eight times in eukaryotes (Jékely, 2009).

Compared to the number of organisms that rely on DHA, the number that are able to synthesize and accumulate DHA de novo efficiently is rather limited. The main producers of DHA are the Bacillariophyceae, Cryptophyceae, Dinophyceae and Prymnesiophyceae, which primarily inhabit oligotrophic aquatic ecosystems (Aligren et al., 1996; Taipale et al., 2016). Besides microalgae, thraustochytrids, belonging to the kingdom Chromista and closely resembling a zoosporic fungi, are able to accumulate significant amounts of DHA (up to 12.5% of their dry mass), however, their total ecosystem biomass, as a saprophyte, is rather low (Kimura et al., 2001; Raghukumar, Ramaiah & Raghukumar, 2001; Fan et al., 2007; Lee Chang et al., 2012). Eutrophication leads to an increase in density of cyanobacteria and this decreases the trophic transfer of LC-PUFA to higher trophic levels and, consequently, the nutritive quality of fish for human consumption (Müller-Navarra et al., 2004; Taipale et al., 2016). However, it should be noted that total LC-PUFA production increases with the availability of nutrients and in many eutrophic lakes cyanobacteria blooms typically occur in summer. When considering an entire year, the highest availability of LC-PUFA is found in mesotrophic waters (Müller-Navarra et al., 2004; Gladyshev, 2018). Furthermore, it has to be considered that other factors, such as dissolved organic matter and underwater light availability can alter the trophic pathways of EPA and DHA and influence the amount of LC-PUFA available for consumer (Senar et al., 2019).

In terrestrial primary producers, only some soil algae, lichens and some mycorrhizal and saprotrophic fungi are able to produce considerable amounts of LC-PUFA de novo and their contribution in relation to global LC-PUFA production is therefore negligible (Rillig, 2004; Kaštovská et al., 2007), as is the production of EPA in some nematodes, either de novo or by their gut microflora (Sampedro, Jeanotte & Whalen, 2006; Menzel et al., 2019). Terrestrial higher plants do not have the ability to synthesize LC-PUFA (Sayanova & Napier, 2004; Ward & Singh, 2005; Ruiz-López et al., 2012) and strictly herbivorous terrestrial animals must therefore rely on conversion (‘trophic upgrading’). This is beneficial for higher consumers that prey on these animals, with especially their liver and brain tissues providing a source of LC-PUFA for carnivorous animals (Stark, Crawford & Reifen, 2008; Gladyshev & Sushchik, 2019).
(2) Trophic transfer and possible ramifications of fluctuations

As signalling efficiency by GPCR is enhanced when embedded into lipid non-raft domains generated by DHA, or other omega-3 PUFA, the acquisition of these PUFA is key to the development of optimally functioning neurological structures. However, there is also an increased cost, as the brain is an expensive tissue to maintain and accounts for a significant share of the basal metabolic rate (Isler & Van Schaik, 2014). Therefore, saving energy by not requiring de novo synthesis of essential fatty acids and maintaining the associated biochemical production cycle generates an evolutionary advantage. On the other hand, it generates a dependency on dietary food sources that are able to supply enough DHA for the increased amounts required.

In general, aquatic ecosystems are regarded as the main producers of DHA in the biosphere (Gladyshev, Arts & Sushchik, 2009). It has been suggested that trophic transfer of DHA produced by aquatic sources and transferred via non-arthropodous supply chains meets the requirements of terrestrial consumers (Gladyshev, Arts & Sushchik, 2009), implying that, under certain conditions (e.g. anthropogenic stress), omega-3 PUFA may become a limiting factor in ecosystems (Závorka et al., 2019). Compared to the transfer efficiency of dietary energy of about 10% for each level, the efficiency for the transfer of PUFA is 2–5 times higher, underlining their dietary importance (Pauly & Christensen, 1995; Broadhurst et al., 2002; Plourde & Cumnane, 2007; Gladyshev et al., 2011). DHA is transferred to the terrestrial ecosystem either through direct consumption of aquatic prey by riparian predators, emergence of amphibioutous insects, drift of carrion and seaweeds, water birds or through human fisheries (Gladyshev, Arts & Sushchik, 2009; Gladyshev, Sushchik & Makhutova, 2013; Martin-Creuzburg, Kowarik & Straile, 2017).

The Intergovernmental Panel on Climate Change estimates that, by the end of the 21st century, the temperature of inland waters may rise by an average of 4°C (Field et al., 2014; Sanderson et al., 2017), which, together with an increase in water brownification, may lead to a shift in the diversity of plankton, particularly towards taxa (e.g. cyanobacteria) with low LC-PUFA content (Rasconi et al., 2015; Rasconi, Winter & Kainz, 2017). This will inevitably have significant consequences for the entire aquatic food chain, which cannot yet be predicted accurately because there is a lack of knowledge on how LC-PUFA supplies are altered by shifts of algal taxa and changes in LC-PUFA synthesis capabilities, how LC-PUFA retention is altered by consumers, and how this affects consumer behaviour (Jin, González & Agustí, 2020). In general, higher water temperatures lead to decreased primary production of LC-PUFA (Colombo et al., 2019), as well as reduced retention in consumers (Kákelá et al., 2008; Werbrouck et al., 2016) Thus, sustaining DHA supply for humans will remain critical for the future.

While there is some literature about the effect of omega-3 PUFA deprivation derived from laboratory experiments, field studies that systematically investigate the eco-evolutionary implications of diet quality are scarce and are only recently gaining traction. In this context, besides the already discussed decrease in visual acuity or altered evasion strategies with significant potential to affect predator–prey interactions, spatial orientation and navigation, which both demand high sensory and memory capabilities, might be crucial traits affected by diet quality. For example, many mammals store food in caches. These hidden food stores are directly linked to their survival and it has been shown that dietary DHA improves their spatial memory and increases their ability to remember where their caches of food were hidden (He et al., 2009; Wang et al., 2018). Furthermore, predators, particularly those with large home ranges, must have a detailed spatial map of their hunting area with intimate knowledge and memory of key signposts; i.e. they must be able to remember where and when to hunt in order to maximize success. If any of these mental abilities are impaired due to inadequate signalling fidelity, caused by reduced access to DHA, then their hunting success rate should diminish (Benhamou, 1994; Noda, Gushima & Kakuda, 1994; Takahashi & Sato, 2017). Last, but certainly not least, there is the conspicuous and very important phenomenon of bird, fish, and mammal migrations, which affect ecosystems all around the globe (Quinn, 2018; Fleming, 2019; Hegemann, Fudickar & Nilsson, 2019; Rosenberg et al., 2019). For example, there is a direct link between dietary PUFA and the timing of bird migration stopovers; a critical aspect of bird life history (Schnurr et al., 2020). Aquatic insects richer in LC-PUFA have demonstrable effects on the growth rate and body condition of chicks, which is reflected in higher EPA content in bird muscle and brain tissues (Dodson, Moy & Bulluck, 2016; Twining et al., 2016). Similarly, anadromous fish transport an incredible amount of EPA and DHA from oceans into rivers, streams and lakes, while also relying on spatial orientation and memory (Odling-Smee & Braithwaite, 2003; Gladyshev et al., 2018; Quinn, 2018). Multiple studies have demonstrated the huge effect of diet quality on brain development of fish (e.g. Ishizaki et al., 2001; Oberg & Fuiman, 2015), which, by changing cognition, might also affect their migratory patterns (Kolm et al., 2009). In combination with increased hydrologic variability and anthropogenic effects (Ward et al., 2015), alteration of migratory patterns could also severely impact the local availability of LC-PUFA.

(3) DHA production for human consumption

For humans, an increasing gap between PUFA production and consumption has been identified, arising, in part, due to massive increases in population during recent centuries (Tocher et al., 2019; Hamilton et al., 2020). It is estimated that just ~5% of dietary consumed ALA is converted to LC-PUFA, excluding pregnant females, which is unlikely to provide a sufficient level of DHA supply throughout the human lifespan (Davis & Kris-Etherton, 2003; Burdge, Tan & Henry, 2017). Higher levels of DHA are found in young environments, and increased levels of DHA have been shown to be associated with increased learning and memory performance in children (O’Brien et al., 2016).
women and oestrogen has been shown to induce epigenetic modifications specifically in the chromosomal region containing the FADS1 and FADS2 genes, encoding Δ5-desaturase and Δ6-desaturase, respectively. This might be an evolutionary mechanism to increase conversion of ALA to DHA during pregnancy and subsequently increase DHA plasma levels for the development of the fetus (Gilley et al., 2004a, 2004b, Sibbons et al., 2014). The World Health Organization (WHO) recommends a daily consumption of 500 mg of EPA and DHA, which is contained, depending on the quality of the fish source, in ~50 g of salmon (Colombo & Mazal, 2020). LC-PUFA for food supplementation are mainly derived from fish oil, however, the formulation is very important as free fatty acids are more bioavailable than triacylglycerols (TAG) or ethyl esters (Davidson, 2013; Ghasemifard, Turchini & Sinclair, 2014). Total annual production of LC-PUFA is estimated to be ~0.8 million tons, compared to the required production of 1.4 million tons to meet WHO recommendations for the global population (Hamilton et al., 2020). The main source of DHA is fisheries (both wild and, increasingly aquaculture), but many wild stocks are fully exploited and 63% of fish stocks urgently need rebuilding (Worm et al., 2006).

Possible ways to increase DHA supply to humans in the future are to increase the efficiency of aquaculture and/or introduce biotechnological production methods involving microorganisms and genetic engineering. However, each of these strategies has its own limitations. Demands for fish from aquaculture are continuously increasing (FAO, 2018), however, they are also a major consumer of DHA: salmonids require fish oil and fish meal themselves (Tocher, 2010). The increase in price for fish oil has led to partial substitution with plant ingredients (Adarme-Vega, Thomas-Hall & Schenk, 2014; Tocher et al., 2019), which could reduce the consumption of LC-PUFA by about 6%, but at the cost of DHA content in farmed salmon (Sprague, Dick & Tocher, 2016). While there are some attempts to bridge the gap between supply and demand and to unlock sustainable sources of omega-3 LC-PUFA, a better understanding of the lipid metabolism throughout an aquatic ecosystem, as well as an increased by-product utilization and food waste prevention could lead to more efficient transfer of these limited resources and contribute to higher quality of fish for human consumption (Hamilton et al., 2020). Furthermore, there are also aquaculture species (e.g. molluscs and carp) which naturally accumulate DHA (and/or its precursors) directly from the environment (Pauly & Christensen, 1995; Rodrigues et al., 2017). Thus, consuming DHA from a lower trophic level, increasing non-fed fish farming or diverting more wild catch to human consumption might be more efficient strategies for DHA transfer from natural resources to humans (Hamilton et al., 2020).

Microorganisms are considered the most attractive source for large-scale production of DHA, however, bacteria do not accumulate DHA in triacylglycerols, and production via photoautotrophic microalgae is limited by achievable density due to light limitation, oxygen accumulation and/or temperature regulation (Sijtsma & de Swaaf, 2004; Mendes et al., 2009; Sprague, Betancor & Tocher, 2017). Several transgenic plants have been generated that produce EPA and DHA, however, reaching economically viable levels has proved difficult (Robert, 2006; Damule & Kinney, 2007; Ruiz-López et al., 2012; Sprague, Betancor & Tocher, 2017) and large-scale cultivation may have serious impacts on local ecosystems that must be carefully considered (Beacham, Sweet & Allen, 2017; Sprague, Betancor & Tocher, 2017; Colombo et al., 2018).

V. CONCLUSIONS

(1) De novo synthesis capabilities and requirements for DHA have co-evolved with transmembrane receptors, in particular GPCR, such as rhodopsin which is important for vision or dopamine and serotonin receptors that function in cognition, mood, behaviour and memory.

(2) Co-evolution of metabolic availability of DHA across food chains and GPCR led to enhanced cognitive abilities, but created dependencies on primary producers of PUFA, as these metabolically expensive tissues required cost savings in metabolic production cycles for a net gain in ecological fitness.

(3) A chronic deficiency of dietary omega-3 PUFA affects neurological tissues that are particularly dependent on DHA, e.g. the retina and brain, leading to visual impairment, reduced cognition, memory defects and impaired spatial navigation and might be involved in neurological diseases including mood disorders and dementia.

(4) There is a paucity of studies extrapolating experimental findings to complex natural environments, which will be crucial for understanding these implications from ecological and evolutionary perspectives. Linking molecular mechanisms to potential ecological implications generates new testable hypothesis that ultimately will contribute to a better understanding of dietary omega-3 PUFA provision to food-web dynamics.

(5) Global LC-PUFA production may be insufficient to supply the needs of the growing human population. It is therefore important to understand better how and where DHA is synthesized in organisms of aquatic and terrestrial food webs, and how humans will be supplied, in the not so distant future, with enough DHA to satisfy requirements for human health.

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Omega-3 PUFA, neurophysiology and ecology

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