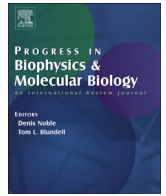




Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

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

From cholesterol to consciousness

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ARTICLE INFO

Article history:

Received 14 July 2017

Received in revised form

16 August 2017

Accepted 18 August 2017

Available online xxx

Keywords:

Consciousness

Calcium flux

Target of Rapamycin

Cytoskeleton

Cell-cell communication

ABSTRACT

The nature of consciousness has been debated for centuries. It can be understood as part and parcel of the natural progression of life from unicellular to multicellular, calcium fluxes mediating communication within and between cells. Consciousness is the vertical integration of calcium fluxes, mediated by the Target of Rapamycin gene integrated with the cytoskeleton. The premise of this paper is that there is a fundamental physiologic integration of the organism with the environment that constitutes consciousness.

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“Life is that which can mix oil and water”- Robert Frost

1. Introduction

A unique cellular-molecular approach to physiologic evolution has proven to be predictive for otherwise opaque, dogmatic aspects of biology (Torday and Rehan, 2012). For example, it has led to the realization that ‘life is simple’ (Torday, 2016). We complicate it due to our subjectively evolved senses, which David Bohm (1980) referred to as the ‘explicate order’; in contrast to this, the

‘implicate order’ is a deeper more fundamental view of reality. By viewing the life cycle from the perspective of the germ cells and zygote as the primary level of selection, the offspring can be viewed as an ‘agent’ for obtaining epigenetic marks (Torday and Miller, 2016a). In this frame of reference, the unicellular state is a point source (Torday and Miller, 2016b), perpetually maintaining equipoise by communicating with its surroundings. If the unicell is perceived as the author of our being, life literally could not be simpler. This holds true at every level of life as non-scaler when seen from its origins instead of its consequences (Torday and Rehan, 2012, 2017). That includes the nature of consciousness, which has been debated for centuries (Torday and Miller, 2016c). The proposed mechanism of consciousness only applies to biological organisms on Earth. It does not preclude other mechanisms of

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<http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.009>
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Please cite this article in press as: Torday, J.S., From cholesterol to consciousness, Progress in Biophysics and Molecular Biology (2017), <http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.009>

consciousness that could arise in non-biological systems, including manmade machines or extraterrestrial organisms.

Many philosophers think that there is a shared understanding of what consciousness is (Searle, 2005). Since the time of Plato, philosophers have tried to understand the properties of consciousness. Thoreau reconciled the mind body duality formulated by Descartes by going to Walden Woods and living his life deliberately (Tauber, 2003). Others have tried to determine the mechanism of consciousness (Hameroff and Penrose, 2014), whether non-human consciousness exists (Griffin, 2001), the relationship between consciousness and language (Searle, 2002), whether consciousness can be understood other than as a dualistic distinction between mental and physical states or properties (Dy, 2001), or whether hominin-like artificial intelligence is feasible (Hutter, 2005).

When seen as an exaptation (Gould and Vrba, 1982), or pre-adaptation, starting with the presence of lipids in the primordial oceans delivered to Earth by frozen snowball asteroids (Deamer, 2017), consciousness can be understood as part and parcel of the natural progression of life from unicellular to multicellular. The premise of this paper is that there is a fundamental physiologic integration of the organism with its environment that constitutes consciousness. In order to achieve this integration, life formed a self-organizing, self-referential structure, the unicell, by delineating the internal and external environments using a semi-permeable lipid membrane (Deamer, 2016). Within that space negative entropy was made possible by chemiosmosis, or the movement of ions across a selectively permeable membrane, down their electrochemical gradient, (Mitchell, 1961), regulated by homeostasis (Cannon, 1939). Based on these First Principles of Physiology (Torday and Rehan, 2012), cell-environment and cell-cell interactions have fostered vertebrate evolution over the course of the last 4.5 billion years. Under 'stress' the cellular interactions have changed in order to alleviate it, within the constraints of the pre-existing physiologic conditions. Ultimately, a new equipose was reached due to evolution.

There is empiric precedence for sterols in the primordial oceans (Deamer, 2017). And since evolution is constituted by serial exaptations/pre-adaptations, the use of cholesterol was based on those pre-adaptive origins of lipids for life to emerge. The homology between lipids and oxygen reappeared when oxygen caused endoplasmic reticulum stress, resulting in calcium leakage into the cytoplasm (Mekahli et al., 2011). In order to counterbalance that existential threat, peroxisomes evolved (De Duve, 1969) and buffered the excess calcium using lipids. Lipids were later used as the basis for the synthesis of both steroid endocrine hormones and Vitamin D (Griffiths et al., 2017). As for progress in understanding the evolution of the central nervous system (CNS) as the seat of consciousness, it had been at a standstill for many years since there was a gap between knowledge of the CNS of invertebrates and vertebrates. However, Nick Holland pointed out that the central nervous system of invertebrates was present in their skin, giving rise to the 'skin-brain' hypothesis (Holland, 2003). In support of this hypothesis, there are some interesting homologies between the skin and brain, both forming lipid 'barriers'. In the case of the skin, the stratum corneum secretes lipids to prevent loss of bodily fluids and protection against bacterial invasion (Aberg et al., 2008). The Epidermal Growth Factor (EGF) signaling family also promotes epithelial barrier formation (Barrientos et al., 2008). Similarly, the EGF signaling pathway regulates lung alveolar formation by promoting lung surfactant production (Fiaturi et al., 2014). In the brain, Schwann Cells enshroud neurons with lipids to make calcium ion flux efficient (McKenzie et al., 2006). Schwann Cells express Neuregulin, which binds to the neuron to promote lipid deposition for myelination (Feltri et al., 2016).

These molecular homologies are underscored by pathophysiologic relationships between the skin and brain, and between the

lung and brain. All of the neurodegenerative diseases have skin homologs (Chou et al., 2017). And the Defensin mutation that causes asthma also causes atopic dermatitis in the skin (Chieosilapatham et al., 2017).

2. From cholesterol to neurons

Cholesterol is the archetype for this process. Initially sterols were present in the frozen water composing the asteroids that formed the oceans on Earth (Deamer, 2017). In water, sterols spontaneously form micelles, semi-permeable cell membrane spheres within which the First Principles of Physiology could form (Torday and Rehan, 2012). Cholesterol synthesis emerged under the stress of rising oxygen in the atmosphere as a means of protecting primitive cells from oxidant injury (Csete et al., 2001). The insertion of cholesterol into the phospholipid bi-layer thinned the cell membrane (McIntosh, 1978), increasing oxygenation, metabolism and locomotion (cytoplasmic streaming). Subsequently, cholesterol formed lipid rafts in the cell membrane, forming the basis for receptor-mediated signaling (Thomas et al., 2004). Ultimately, this process culminated in the endocrine system of complicated vertebrates. When cholesterol is interfered with in the cell, the critical processes that contribute to consciousness (detection, decision, action) break down (Pfrieger, 2003).

Therefore, cholesterol plays a fundamental role in consciousness. The lipid micelles suspended in water were heated by the Sun during the day, and cooled at night, causing them to deform and reform faithfully because they exhibit hysteresis, or molecular memory. This may have been the physical-chemical connection between the 'conscious order' formed by the Big Bang (Priogine and Stengers, 1984) and biological consciousness, since evolution requires memory in order to determine whether to remain at equipose or change under any given environmental condition.

There are hypothetically predictive implications for this fundamental relationship between lipids, memory and consciousness. Although hypercholesterolemia is recognized as a risk factor for atherosclerosis and heart disease (Johnston et al., 2017), the cause of cholesterol dyshomeostasis is poorly understood, particularly during the process of aging (Seo and Choi, 2015). Moreover, cholesterol is necessary for synaptogenesis (Pfrieger, 2003), particularly recognizing the 'neuroplasticity' of the brain (Bennett et al., 1964). And Cochran et al. (2006) have shown the fine balance between too much lipid and neurodegenerative disease. A fundamental, evolutionary basis for cholesterol metabolism would benefit understanding all of these conditions.

Bloch hypothesized that cholesterol was synthesized once there was adequate oxygen in the atmosphere since it takes 11 atoms of oxygen to synthesize one molecule of cholesterol (Bloch, 1992, but see Waldbauer et al., 2011). But given that evolution is constituted by serial exaptations (Gould and Vrba, 1982), the use of cholesterol in the cell membrane of evolving unicellular eukaryotes hypothetically had an ancestral antecedent. When immersed in water, lipids spontaneously form primitive 'cells', or micelles, semi-permeable membrane spheres. The partitioning of free energy between the cell and its environment was a quantum leap from the inanimate to the animate (Deamer, 2017).

Calcium levels in the oceans increased due to rising levels of atmospheric carbon dioxide dissolving in the water, forming carbonic acid, which caused leaching of calcium from the bedrock (Case et al., 2007). Initially, in combination with calcium channels (Torday and Rehan, 2012), unicellular organisms were able to entrain intracellular calcium (Case et al., 2007). Subsequently, oxidant stress caused endoplasmic reticulum stress, the resulting calcium leakage into the cytoplasm giving rise to peroxisomes (De Duve, 1969), the organelles that protect the cell against such excess calcium.

The calcium fluxes that determine human activity and thought in the peripheral and central nervous systems are no different from those in a paramecium responding to glucose in water (Klauke et al., 2000), since the sensing of nutrient is mediated by calcium flux in both cases (Aamodt and Constantine-Paton, 1999).

The mere fact that we return to the unicellular state iteratively infers that consciousness is the integration of mind and body, calcium ions passing through the cell (Aamodt and Constantine-Paton, 1999) to determine physiologic function. We return to the unicellular state iteratively in order to inform the germ cells of what the organism has gleaned from the environment epigenetically by means of 'marks' (Messerschmidt et al., 2014). Such marks are processed during meiosis (Kota and Feil, 2010), reflecting consciousness of the integration of mind and body, consciousness originating from the Cosmos (Bucke, 2009; Normandin and Wolfe, 2013). Functionally, the continuum from the calcium burst at conception (Santella et al., 2004) to the calcium fluxes that constitute being (Brini et al., 2014) is the chemical embodiment of that conscious merging of the physical and the biological into one continuous process, like Abraham Maslow's 'peak experiences' (Maslow, 1964). In fact, when the sperm fertilizes the egg there is a calcium burst that initiates the division of the zygote and the ensuing embryogenesis (Cohen et al., 2014). The fact that the epigenetic process glean information from the environment and stores it in the germ cells culminates in such a calcium burst, excluding all other such interactions (Cuasnicú et al., 2016) infers a discrete event by which the offspring becomes conscious of its surroundings. Yet the germ cells themselves may also be considered conscious, given that they exhibit a way of discerning which epigenetic marks to retain during meiosis (Morgan et al., 2005; Santos et al., 2005; Taguchi, 2015). Embryogenesis facilitates this process by determining whether any given epigenetic mark is compatible with the homeostatic state of the embryologic structure or function being formed (Richardson and Keuck, 2002). And even after birth, the stages of the life cycle themselves are modified by the endocrine system of the organism, determining the length and depth of any given stage (Zhang and Ho, 2011) as the mechanism by which epigenetic marks are collected in a physiologically context-sensitive manner. Consider for example the Piagetian perspective on the extended childhood of hominins, seen as a way of collecting epigenetic marks for neurologic development (Beilin and Fireman, 1999). It is conventionally thought that hominin infancy and childhood are protracted because it takes a long time to develop our relatively big hominin brains (Johnson, 2001) based on descriptive biology; however, from an epigenetic, mechanistic perspective, this process is protracted in order for the child to acquire relevant epigenetic marks during infancy, crawling, and toddling, respectively, i.e. the passive ex post facto versus the active 'phenotype as agent' view (Torday and Miller, 2016a). Reducing the psychological perspective to the cell-molecular level affords greater opportunity to integrate it effectively with other aspects of physiologic development.

It is easy to conceive of the interrelationship between calcium flux and consciousness as an integrated whole in unicellular organisms, which dominated the Earth for the first 4 billion years of its existence. We now know that multicellular organisms evolved as a result of cell-cell communications mediated by soluble growth factors (de Laat et al., 1999).

Signaling is mediated by G-coupled protein receptors that 'amplify' such signals via Protein Kinases, changing the physiologic state of the cell in the process. During development, such signaling mechanisms control the growth and differentiation of neighboring cells of different germ line origins in what is referred to as pattern formation. Once development has been completed, such signaling mechanisms revert to determining homeostatic control of physiology (Torday and Rehan, 2007a, 2012, 2017). These mechanisms of

integrated physiology have evolved over the Phanerozoic Eon, exploiting cell-cell signaling for cell-to-organism allostatic regulation (McEwen and Wingfield, 2003). From this vantage point, the role of calcium flux in sensing internal and external change can be seen as a continuous process of vertical integration from unicellular to multicellular consciousness.

3. Target of Rapamycin, the cytoskeleton and consciousness

3.1. A vertically integrated approach to consciousness

The premise of this paper is that there is a fundamental physiologic integration of the organism with the environment that constitutes consciousness. The cytoskeleton determines the entire phenotype of the cell-homeostatic, meiotic and mitotic. It is functionally interconnected with and controlled by the Target of Rapamycin (TOR) gene, which in turn is interconnected with many aspects of cell biology-replication, metabolism, ion concentration, oxidants (Dobashi et al., 2011). TOR is expressed in a wide variety of organisms, ranging from mammals (Dobashi et al., 2011), to yeast (Heitman et al., 1993), *Dictyostelium* (David, 2011), and *Drosophila* (Zhang et al., 2006). As a centralized mechanism for sensing the environment, both internal and external, TOR acts like a molecular conscience. The TOR gene is the final common pathway for integrating all aspects of cellular existence. As such it functionally constitutes the consciousness of the cell, and its cellular signaling partners, maintaining homeostasis within and between tissues, organs and the organism as allostasis (McEwen and Wingfield, 2003). Given the pleiotropic relationships between visceral organs, and between the viscera and central nervous system (Torday, 2015b), this is the functional definition of consciousness.

Specific phenotypic examples are offered herein, ranging from food restriction to microgravity or zero gravity.

3.2. *Dictyostelium*, the environment and mTOR

The slime mold *Dictyostelium discoideum* exists in binary phenotypic states-the free-living, locomotor amoeboid form, and the sessile, colonial form. These two states of being are determined by nutrient availability, abundance causing the amoeboid form, paucity the colonial form. Seen from the perspective of epigenetics, the locomotor form promotes the active collection of epigenetic 'marks' by the phenotype as agent (Wang et al., 2017). Conversely, the colonial form passively derives epigenetic marks from the environment based on its immobile state.

The underlying mechanism for this environmentally determined phenotypic expression of locomotor versus sessile life is the TOR gene (Lee et al., 2005). The TOR gene determines these phenotypic differences by controlling the conformation of the cytoskeleton (Huang and Fingar, 2014). Thus, being conscious of the environment can be seen as signal transduction of nutrient abundance, translating into phenotypic expression of the cytoskeleton.

3.3. Food restriction, consciousness and mTOR

In mammals, food restriction is associated with longevity (Finkel, 2015). This phenomenon is interpreted as the etiology of disease since the offspring exhibit Metabolic Syndrome, namely diabetes, hypertension and obesity-all of which are largely age-dependent. However, the effect of this manipulation on puberty is overlooked; the offspring are also growth-restricted, causing precocious adrenarche, an early phase of sexual maturation in primates, and sexual maturity (Longo et al., 2013). Therefore, the primary effect of food restriction may actually be on the ability to reproduce, offering the opportunity to shorten the latent period

prior to puberty in order for the offspring to rapidly advance to the hopefully food abundant environment. Logically, it is assumed that *D. discoideum* evolved in a relatively abundant nutrient environment, compatible with a mobile phenotype, the immobile colonial phenotype being a way to pragmatically preserve the organism in low food abundance conditions.

3.4. Gravity links to consciousness through mechanotransduction

There are several examples of gravity affecting physiology. The classic example is its effect on bone, referred to formally as Wolff's Law (Wolff, 1986). When strain is applied to bone it will remodel to alleviate the stress by decalcifying and subsequently recalcifying due to decreased or increased Parathyroid Hormone-related Protein (PTHrP) mRNA expression, respectively (Wongdee et al., 2012). When osteocytes are exposed to microgravity PTHrP gene expression decreases due to altered TOR signaling (Yan et al., 2016).

Further to the relationship between gravity and consciousness, yeast are unicellular eukaryotes; when they are exposed to microgravity they lose their ability to polarize and bud (Purevdorj-Gage et al., 2006). Without such properties, these organisms are essentially in a state of suspended animation because they cannot mediate calcium flux (polarization), or reproduce (loss of budding). Hence, they are 'unconscious', again demonstrating the link between gravity, the cytoskeleton and consciousness.

4. Discussion

Teilhard de Chardin (2015) and Gurdjieff (Churton, 2017) conceived of consciousness as a continuum from the simplest to the most complicated life forms, as expressed in Bucke's "Cosmic Consciousness" (Bucke, 2009). This is an attractive concept, but without a mechanistic basis, it remains speculative at best. But with the recognition of the ontology and epistemology of consciousness reduced to calcium flux, constrained by lipids, consciousness as the means by which the organism perceives the external environment is tractable and experimentally testable, independent of scale. It becomes yet another derivative of the First Principles of Physiology, a manifestation of negentropy, or negative entropy, chemiosmosis, and homeostasis (Torday and Rehan, 2012).

As such, the functional integration of physiology from its very origins, both phylogenetically and ontogenetically alike offers the opportunity to conceive of consciousness as serial exaptations (Gould and Vrba, 1982), like those that have formed other physiologic traits such as the lung (Torday and Rehan, 2007b), kidney (Torday and Rehan, 2012) and other viscera (Torday and Rehan, 2012). In a recent paper (Torday and Miller, 2016c), the interrelationship between endothermy and the evolution of the mammalian brain was expounded on. This capacity is shared by mammals and birds alike, enabling them to range far and wide, relatively unimpeded by environmental variations in such aspects of the environment as temperature, terrain and rainfall, affording them equally widely varied exposure to epigenetic marks-witness the Albatross flying transglobally, or hominins leaving the Earth's gravity. Brain cooling is a truly liberating experience for consciousness, rendering it 'higher' in its capacity to acquire epigenetic marks for these species.

Relating the evolution of warm-bloodedness to consciousness forms the physiologic linkage between the nervous system and the viscera, all ascribing to cell-cell communication (Torday, 2015a). This cellular-molecular level of integration provides the opportunity to conceive of mind and body acting in concert from their very origins in the unicellular state, moving forward in time and space evolutionarily (Torday and Miller, 2016b). This process is reinforced by the reconceptualization of pleiotropy as the way in which genes

have been exploited, being repurposed evolutionarily to address changes in environmental conditions (Torday, 2015b). For example, Neuregulin is an intermediary in the Epidermal Growth Factor signaling pathway that is found in both the lung and brain, regulating lipid utilization in both: in the lung it determines lung lipid for surfactant production (Fiaturi et al., 2014); in the brain it determines lipid myelination of neurons by Schwann Cells (McKenzie et al., 2006). This is a prime example of how mind and body are functionally integrated.

Consciousness has been viewed in this light phenomenologically by others. For example, as reflected by the way in which patients recover from general anaesthesia, seemingly recapitulating brain phylogeny (Mashour and Alkire, 2013). Candace Pert has speculated how the body 'speaks' to the brain via 'Molecules of Emotion' (2010). Hughlings Jackson, the British neurologist developed a way of understanding the evolution of the nervous system as three levels: lower, middle and higher (Phillips, 1973). He thought that the 'higher' centers inhibited the lower ones, and that failure to do so disinhibited the lower centers, causing brain pathology.

Such holistic ways of thinking about the nature of consciousness can now be reconsidered at the cellular level mechanistically instead, offering the opportunity for experimental testing and refutation. For one thing, if you deconvolute consciousness it offers the opportunity to transcend the explicate order and approximate the implicate order as objective truth (Bohm, 1980). In so doing, we would gain a greater understanding of our own species and that of other species. Equally importantly, it would allow us to appreciate our surroundings as the resources that we have evolved to interface with, both locally, and globally as Gaia (Lovelock, 1972). The philosophers have been in this camp since Plato's Timaeus (Cornford, 1935), or even earlier, primitive hunter gatherers painting animals on cave walls at Lascaux (David and Lefrere, 2014). From that time to this we have expressed the desire to be at one with ourselves and our surroundings, instead mistaking material effects as causes-materialism, pleasure seeking, the arts, religion-all instead of seeking the truth of our very being (Whybrow, 2006).

Acknowledgements

JST has been supported by NIH grant HL055268.

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