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From membrane excitability to metazoan psychology

Norman D. Cook[1,2], Gil B. Carvalho[2], and Antonio Damasio[2]

[1] Department of Informatics, Kansai University, Osaka 569-1095, Japan
[2] Brain and Creativity Institute, University of Southern California, Los Angeles, CA 90089-2921, USA

Unlike the nonexcitable cell membranes that are ubiquitous in all domains of life, excitable membranes are found almost exclusively in animal organisms (Protozoa and Metazoa). Their transient permeability to ion flow makes possible the rapid detection of, and response to, external stimuli, and results in the phenomena that most clearly distinguish fauna from flora: perception, cognition, and motor activity. Interestingly, all known forms of membrane excitability are a consequence of one unique mechanism: the influx of positively charged ions into the normally alkaline cytoplasm. Here, we suggest that the sudden reversal of the membrane potential during the sensory potential and the action potential is an electrostatic disturbance of homeostasis that is the necessary first step in the processes of 'sentience' and 'irritability'.

From cellular excitability to animal psychology

The importance of excitable membranes was understood implicitly in early research on both unicellular protozoan organisms (Protista) [1,2] and the neurons of multicellular metazoan organisms (animals) [3], but did not become explicit until the electrophysiological discoveries on transmembrane ion movement during the mid-20th century [4–6]. Over the past two decades, the molecular structure of ion-channel proteins [7,8] and their evolutionary genetics [9] have been largely elucidated and it is now apparent that the influx of cations across semipermeable membranes is the mechanism that underlies the excitability of: (i) sensory receptor cells; (ii) neurons; and (iii) muscle cells in all animal organisms.

Clarification of the important role of the ion-channel proteins in membrane excitability has been a remarkable achievement of 21st-century molecular biology, but the significance of that achievement is not widely appreciated beyond a few channel protein specialists. Here, we summarize evidence supporting the idea that the influx of positively charged ions during membrane excitability is the unique cellular phenomenon that underlies all aspects of animal psychology.

Homeostasis

Biological cells are enveloped by plasma membranes that act as hermetic seals to keep cellular organelles in and external materials out. Indeed, 'discrimination between inside and outside is the first structural prerequisite for the living cell and the living in general' ([10] p. 185). The cell membrane also allows the intracellular cytosol to be kept in physiological conditions through the active transport of cations (H^+, Na^+, and Ca^{2+}) out of the cytosol, thus ensuring a mildly desalinated, mildly alkaline (pH 7.6±0.2) internal milieu [11]. So-called 'extremophile' bacteria and Archaea have adapted to harsher extracellular environments, but even they maintain a neutral biochemical intracellular state [12] for the over-riding reason that macromolecules lose their higher-order structure in strongly acidic, alkaline, or saline solutions and become dysfunctional [13]. Therefore, one of the primary functions of the plasma membrane is to maintain homeostasis for all cells from the three domains of life. Homeostatic conditions are of such primary importance for cellular life that the ion channels have been characterized as 'the gatekeepers of the cell' ([14] p. 51) in allowing the selective flow of electrostatic charge into and out of the cell.

Given that the extracellular fluid surrounding protozoan and metazoan cells is often acidic and, moreover, because the oceans during the early evolution of unicellular life are presumed to have been saltier and more acidic than today ([15] p. 31), cells have evolved channel mechanisms to detect and regulate the influx of 'seawater' cations (Figure 1). As a consequence, whenever excessive positive charge accumulates in the cellular interior, excitable cells respond immediately with the repair of ruptured plasma membranes and either protozoan motility, which will extricate the cell from an environment with unfavorable biochemical characteristics, or metazoan muscular contraction, leading to motor behavior of the whole organism. The mechanisms used by excitable membranes to allow for such responses are best understood from the study of the three types of excitable cell that are abundant in animal organisms: sensory receptor cells, neurons, and myocytes. From the perspective of the evolution of life on Earth, it is of profound interest that all of these cells utilize the same general mechanism of excitability to allow rapid, transmembrane cation influx primarily through voltage-dependent sodium and calcium channels [16]. The relevant channel proteins had already evolved in Protists approximately 1 billion years ago, and have subsequently been utilized extensively for intercellular communications in animal organisms (Figure 1B).

Corresponding author: Cook, N.D. (nc_876@usc.edu, cook@res.kutc.kansai-u.ac.jp).
Keywords: excitable membranes; cations; homeostasis; feeling; consciousness.

0166-2236/
 http://dx.doi.org/10.1016/j.tins.2014.07.011

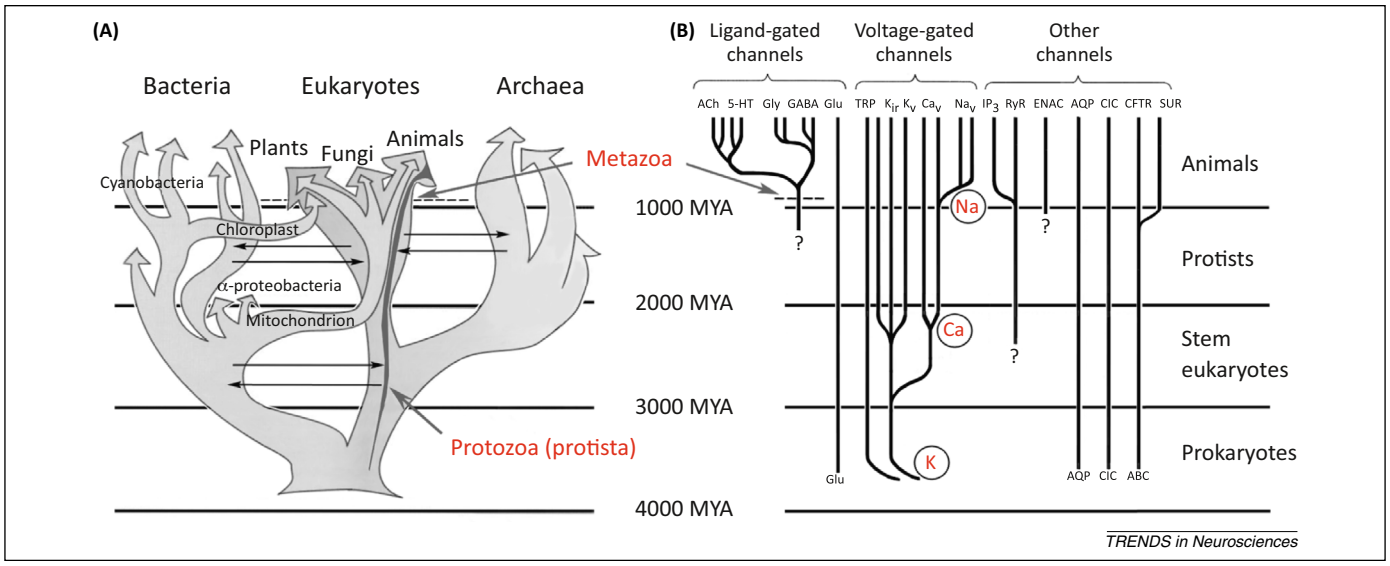

Figure 1. The evolution of excitable membranes. **(A)** All biological cells have evolved mechanisms to maintain homeostasis by means of the relatively slow and energy-consuming import–export of ions and molecules. Reliance solely on such tight biological control has been the evolutionary path followed by most plant cells, many unicellular organisms, and animal cells that do not have excitable membranes. However, an additional path that allows for active responses to external stimulation on a millisecond timescale has also evolved in animal cells with excitable membranes. The path of excitability (in red) is thought to have begun early in the evolution of life on Earth and is in evidence today in both Metazoa and Protozoa. Unicellular Protozoa emerged several billion years ago and have evolved into diverse types, most of which have not yet been satisfactorily classified, let alone studied [61]. Although Hunt [36] pointed out the unusual sensitivity of Protozoa to calcium rather than sodium ions, current understanding of the evolution of the oceans on Earth [62] indicates why the number of cations driving excitability has increased over evolutionary time. Specifically, the early prebiotic oceans had much higher $CaCl_2$ content, so that the earliest Protozoa evolved in Ca^{2+}-rich aqueous environments. As a consequence, the response of most modern-day Protozoa to external stimulation entails the opening of voltage-dependent Ca^{2+} channels and the influx of calcium, not sodium. However, over the course of the subsequent 1 billion years, during which algae and other photosynthetic unicellular organisms released huge volumes of O_2 into the atmosphere, iron, silicon, and calcium in the oceans were transformed into their oxidized forms (ferrites, silicates, and calcites, respectively), and precipitated out to form the ocean crusts [63]. The oceans themselves became less 'hard' with the gradual disappearance of calcium cations and, with a large reduction in $CaCl_2$ and a continuing abundance of sodium chloride, the ratio of Na^+ to Ca^{2+} gradually increased, reaching a current level of 5000:1 [15]. As a consequence, for metazoan excitable cells that evolved subsequent to approximately 800 million years ago (MYA), the detection of the concentration gradient of sodium ions became a more reliable indicator of the salinity of the extracellular fluid and of the loss of integrity of the plasma membrane. **(B)** The evolution of ion channel types. Potassium (K) channels are thought to have evolved in the earliest prokaryotes 4000 MYA, followed by calcium (Ca) channels at 2000 MYA and sodium (Na) channels at 1000 MYA. Note that the voltage-dependent ion channels (K_v, Ca_v, Na_v, etc.) emerged well before the evolution of the ligand-dependent (i.e., neurotransmitter-activated) ion channels (ACh, 5-HT, GABA, etc.) that are essential for the cognition performed by multicellular neuronal networks. Adapted from [16] with permission.

Excitable sensory receptor cells: perception

All sensory receptor cells respond to external stimulation by allowing the influx of cations (Na^+, Ca^{2+}, K^+ and/or H^+) to produce depolarization, the so-called 'receptor potential' (Figure 2A). In some receptor cells, this potential leads directly to an all-or-nothing action potential (AP), whereas other receptors produce a graded neurotransmitter response that approximately reflects the strength of the sensory stimulation [17,18]. Working against the depolarizing effects of cation influx are the polarizing effects of the efflux of potassium cations and the tonic activity of the Na^+/K^+ pump that exports three sodium ions for every two potassium ions imported. As a consequence of these ion movements, sensory receptor cells are either activated by external stimulation (leading to cation influx, depolarization, and, ultimately, the release of excitatory neurotransmitters that propagate the sensory impulse into the central nervous system) or they remain in a polarized state of inactivity.

Although the varieties of human perception are typically classified under sight, sound, touch, taste, and smell, there are seven physiologically distinct classes of sensory receptor in the animal realm [19]: mechanoreception, chemoreception, nociception, thermoreception, electroreception, magnetoreception, and photoreception. Subvarieties of mechanoreception, chemoreception, and photoreception (e.g., 'light current' in response to photic stimulation in invertebrates and 'dark current' in response to the onset of shadows in vertebrates [20]; Box 1), bring the total to more than 12. Remarkably, all receptor cells respond to external stimulation with the influx of cations into the cytosol through voltage-sensitive transient receptor potential protein channels [9].

Excitable neurons: cognition

The mechanisms of membrane excitability in neurons differ from those of receptor cells in that the dendritic membrane of neurons typically allows cation influx through neurotransmitter-gated Na^+ channels (Figure 2B). Depolarization is suppressed by chlorine anions (in response to the opening of neurotransmitter-gated Cl^- channels) and the continuing effects of the Na^+/K^+ pump that works to polarize the cell; however, when the cell is depolarized to a threshold level at the spike-initiating site, neurons generate APs that normally travel down the axon to the synaptic terminal. Given that the AP itself is powered by the influx of sodium ions (through voltage-dependent Na^+ channels), its magnitude does not diminish over the entire length of the axon, but, after 1 ms, the AP is 'switched off' by the closure of Na^+ channels and the subsequent efflux of K^+ ions (through the opening of voltage-dependent K^+ channels). Interactions among different channel fluxes are complex, but the unidirectional flow of the AP is dominated by the transient intracellular increase in the most abundant cation, sodium. By contrast, glial cells have the same set of expressed channel