Bioelectrostatics: Review of widespread importance in biochemistry

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Abstract

The literature reveals an extensive involvement of electrostatics in biological systems. In our prior articles, supporting evidence was cited from sulfates, volatile anesthetics, electron transport in photosynthesis and molecular electrostatic potential studies with DNA. A recent review addresses the involvement of electrochemistry in cell signaling. According to the theoretical framework, electrostatics is believed to be importantly involved in phosphate action in receptors and cell signaling. The main focus is on energetics associated with bioelectrostatics. Examples include action of enzymes, such as, xylose isomerase, SOD and cytochrome c oxidase. In the membrane area, reports deal with the phospholipase-membrane and the nuclear membrane. Other categories are chromosomes, oxidation by hydroxyl radicals, receptors, Hofmeister effect, and histamine. In addition, electrostatic effects have been examined in the plant kingdom.

Keywords: Bioelectrostatics; Energetics; Force; Receptor; Cell signaling; Phosphates; Mechanism

1. Introduction

Examination of the literature reveals extensive involvement of electrostatics in biological systems. This occurs at a fundamental level since electromagnetic forces are
primarily responsible for the structure of matter from atoms to more complex substances. The electrical aspect also appears to be a vital factor in the evolution of life at the early stages [1]. Electrostatic force, a component of electromagnetic interaction, has played a dominant role in the dynamics of cell division and other biochemical processes in primitive cells with the involvement persisting in modern, highly evolved eukaryotic cells.

Our initial proposal on the importance of bioelectrostatics pertained to receptor–ligand activity [2,3]. Molecular electrostatic potential (MEP) associated with ligands is believed to play a role not only in binding, but also in subsequent activities, such as cell signaling, electron transfer (ET) and radical migration. Powerful fields characteristic of ions are found in numerous, important physiologically active substances, e.g., acetylcholine and zwitterions present in ω-amino acids and GABA. Many hormones incorporate substituents with strong dipoles that also display electrostatic fields. In relation to mode of action, a role was proposed as conduits for electrons and radicals in cell signaling. Also, energetics is deemed to be a significant factor.

This article advances the thesis that electrostatics plays a widespread important function in biological activity. Except for neurotransmission, electrochemistry has not attracted the attention that is merited. First, there is a discussion of electrical phenomena in cell signaling. Little is reported on the mode of action of phosphates, which are widely involved in cell communication. This anion is accommodated within the electrostatic framework. Similarly, sulfation provides the sulfate monoanion. Our prior literature in support of bioelectrostatics is reviewed. The present contribution is mainly concerned with extensive evidence dealing with the importance of energetics. The principal categories are enzymes, membranes and miscellaneous areas. Electrostatics is also a crucial force in plant chemistry. It is logical to associate widespread participation of electrostatic forces with the prevalence of ions and dipolar entities capable of involvement in a variety of biological processes, including receptor chemistry.

2. Prior evidence for bioelectrostatics

Earlier hypothesis reviews document reports on the role of MEP in biological processes [2–4]. Some principal items are provided in the following sections.

In the sulfation category, glycoprotein 1(b) alpha, the ligand-binding subunit of a platelet glycoprotein complex, is sulfated on tyrosine residues [5]. The authors proposed that the substance exerts its influence primarily by contributing negative charges. Baculovirus vector requires electrostatic interactions including heparin sulfate for an episomal area. Electrostatics is also a crucial force in plant chemistry. It is logical to associate widespread participation of electrostatic forces with the prevalence of ions and dipolar entities capable of involvement in a variety of biological processes, including receptor chemistry.

A 2004 review summarizes the present status of electrophysiological effects, and deserves special attention [13]. After a burst of research dealing with electrical coupling, gap junctions became less popular among the neurobiologists vs. the ionic approach. Recent reports have
brought gap junction back into the spotlight, suggesting that this type of cell–cell signaling may be intertwined with, rather than an alternative to, chemical transmission. The thesis is credible because the electromagnetic effects of electrons and radicals in motion should have an influence on positive and negative charges associated with the central nervous system (CNS).

Other articles are related to the electrical framework. Results suggest that nanosecond-pulsed electric fields modulate cell signaling from the plasma membrane to intracellular structures and function [14]. This technology could provide a powerful, unique tool to recruit signaling mechanisms that can eliminate aberrant cells by apoptosis. A 1993 symposium dealt with the bioelectricity of cell signaling [15]. Living creatures can be regarded as complex electrochemical systems that evolved over billions of years. Organisms interacted with and adapted to an environment of electrical and magnetic fields. Humans are now immersed in a man-made environment of such fields whose long-term effects are unknown. Computer models are useful tools for handling electrical details of signaling, including interaction of small numbers of molecules [16]. Molecular domain recombination has been used to generate synthetic switches and scaffolds that can specifically alter input/output relationships and generate novel cell signaling behavior [17]. There is the possibility of rewiring cell-signaling circuits, similar to the rewiring of transcriptional ones.

Useful comparisons can be made with electrical conduction in non-biological systems. In copper, the metal serves as a conduit for electrons. The electrical energy is converted into a useful end result, as may be the case for cell signaling. Electrons and holes are also involved in semiconductor operation. Other examples exist among conducting polymers, e.g. polyaniline, involving transmission by radicals and ions.

4. Phosphates and cell signaling

Phosphorylation is widely involved in cell signaling [3,4]. The process in proteins occurs mainly with tyrosine, serine and threonine residues, with serine being the major one. Protein kinases are responsible for the transfer of the phosphate group from adenosine triphosphate (ATP) to the free hydroxyl group of amino acids. Receptor tyrosine kinases are integral membrane proteins comprising about 20 different classes. Other important members are serine/threonine protein kinase and LDL receptor family proteins. Phosphorylation of lipids involves sphingosine and lysophosphatidate. The process also occurs with inositol, choline and ethanolamine. C-AMP and C-GMP are additional examples in the phosphate category.

The mechanism of cancer mutations was examined with the phosphorinositide-3-kinase catalytic subunit [18]. Charge-charge interaction was proposed as a significant factor. Two important amino acid residues were identified, namely, Lys and Arg which can exist as cationic species. The phosphate functionality contributes an anion. It is likely that electrostatic domains play a role in the action mode.

4.1. Phosphates and receptors

There is an abundance of literature on receptors and phosphorylation [3,4]. Much of the research involves the CNS. A number of reports deal with smaller molecules containing the phosphate unit. Signaling by sphingosine-1-phosphate is by a family of G-protein-coupled receptors that signal through a variety of pathways to regulate cell proliferation, cytoskeletal organization and differentiation. Calcium release via intracellular channels is a central event underpinning numerous physiological processes. This release occurs mainly through activation of inositol triphosphate receptors.

Relevant material may be found in a report on plant hormones [19]. Auxin is a pivotal hormone that regulates gene expression. A receptor study revealed the presence of inositol hexakisphosphate in close proximity to the auxin binding site. The authors suggest a potential role for the phosphate in plant hormone signaling. Hence, we surmise that an electrostatic effect may also be operating at the receptor in the plant arena. An ensuing section provides additional material on plant electrostatics.

4.2. Phosphate mechanism

Concerning mode of action, it is probably not coincidental that the phosphates involved are mono-or di-esters containing at least one free hydroxy group in anion form, possessing a strong electrostatic field. The MEP may operate in several ways [4]. A principal factor involves energetics or forces, which is addressed in a subsequent section. In addition, the field may serve as a conduit or bridge for migration of electrons and radicals in cell signaling. The phosphate field would interact with a variety of electrostatic fields present in protein from ions derived from basic and acidic amino acids, and from strong dipoles from the peptide link, as well as other functionalities. The well-known conduits that function in ET are protein, mitochondria, DNA and water.

5. Sulfates and cell signaling

Sulfation is much less prevalent than phosphorylation [4]. The CC chemokine receptors, which are G-protein coupled, are integral membrane proteins that bind cytokines possessing two adjacent cysteines near the N-terminus. There are currently 10 recognized classes of these receptors. Syndecans are transmembrane proteins that act as co-receptors for G-protein coupled receptors and receptor tyrosine kinases. This class is composed of heparin sulfate proteoglycans, which play an essential role in regulating various pathways during development. Similar to phosphorylation, sulfation entails monoesterification
with preservation of an anion residue and accompanying electrostatic potential.

6. Energetics

Mounting evidence indicates that energy is a significant factor in electrostatic operation. Support is available from studies in a variety of fields including both animal and plant.

6.1. Enzymes

Electrostatic interactions play a key role in enzyme behavior [20]. At a long range, electrostatics steer the ligand to the active site, and at short distances, they provide the local interactions for catalysis. Electrostatic sequence and structure analyses of four enzyme families and one superfamily showed that spatial charge distribution is conserved in all cases.

Several investigations address the influence of electrostatics on the transition state. The effect at the catalytic metal binding site in xylose isomerase was examined [21]. Qualitative argumentation, based on protein electrostatic potential, indicates that the proximity of negative side chains to the substrate significantly reduces electrostatic stabilization of the transition state. With the same enzyme, inspection of the protein electrostatic potential around the reaction intermediates indicated that the main role of bivalent metal ions is electrostatic stabilization of the substrate transition states [22].

A report deals with involvement of arginine in the electrostatics and mechanism of Cu, Zn and SOD [23]. The results provide rationale for an evolutionary selection of the amino acid at position 143. Data indicate that this amino acid is the single most important residue in the enzyme both electrostatically and mechanistically. The highly basic amino acid is readily protonated to a cation with an associated electrostatic field.

A 1998 article deals with the role of electrostatic interactions in cytochrome c oxidase function [24]. An investigation was made of electrostatic involvement in determining the midpoint potential of redox-active metal centers and in influencing the behavior of protonated groups in protein. The results provided insight as to how the charged groups can be stabilized in a low-dielectric environment and how the range of the electrostatic effects can be modulated by protein.

6.2. Membranes

An examination was made of electrostatic contributions to membrane binding affinities [25]. Electrostatic energy differences associated with binding-site asymmetry may be a general feature of electrogenic transmembrane ion pumps.

The effect of Ca on electrostatic interaction of the phospholipase-membrane was analyzed by a computation involving electrostatic profiles [26]. Results demonstrate that Ca ions contribute to stability of the complex, and also they create a favorable electrostatic potential pattern that may facilitate membrane lipolysis.

A biophysical mechanism is proposed for breakdown and reassembly of the nuclear membrane based on electrostatics. An increase in net negative nuclear envelope charge could result from the observed release of Ca(II) from envelope stores. Resultant enhanced electrostatic stress in the membranes may provide sufficient electrostatic energy for their breakdown.

6.3. Other systems

Nanoscale electrostatics are proposed to play a significant role in aster (spindle) assembly and motion, as well as in force generation at kinetochores and chromosome arms for motions during mitosis [27]. The study was extended for a model in which motion produces electrostatic interactions to include force generation at spindle poles. Nanoscale electrostatic interactions can provide the force, localized at kinetochores, spindle poles and chromosome arms, to move chromosomes during mitosis. A number of investigations deal with electrostatic properties of microtubule dimer subunits that extend the reach of electrostatic forces [28]. The asters’ pin-cushion appearance is consistent with electrostatics since electric dipolar subunits will align radially outward about a central charge, with geometry resembling the electric field of a point charge.

Electrostatic effects influence oxidation rates of organic compounds in a system involving the hydroxyl radical as oxidant [29]. Increasing ionic strength and pH decreased oxidation rates by factors consistent with predicted decrease in electrostatic effects.

A report on histamine, which is quite relevant to the electrostatic approach, appeared in 1994 [30]. Electric field values near the N (3)–H bond in histamine and those near substituents in agonists correlate reasonably well with observed activities. The usefulness of electric field mapping for both neutral and cationic species makes the technique particularly suitable for substances involved in the CNS. The amidine moiety in histamine is a comparatively strong base, which can exist at physiological pH in protonated, cationic form with electrostatic potential.

Calculations show that the cation is electrostatically stabilized at the cavity center in the potassium channel [31]. Analysis demonstrated cavity stabilization by a favorable electrostatic field arising from pore helices. Energetics from electrostatic factors have important functional consequences on K(I) channels.

6.4. Plants

Not surprisingly, electrostatic potentials have been examined in the plant kingdom. The force fields, which exist between the earth and the atmosphere can affect plants and animals [32]. Electrostatic stress could cause
genetic changes in plants during their early ontogenetic stages.

A study was made of electrostatics and free-energy transduction in nitrogenase, which catalyzes reduction of nitrogen to ammonia [33]. The analysis indicates that electrostatic interactions play an important role in the substitution of MgADP by MgATP upon reduction of the iron–sulfur–Cys cluster in the Fe protein.

7. Receptor action

G-protein coupled receptors (GPCRs) are a family comprising more than a thousand members. Activated G-proteins initiate signal cascades that control various processes, such as metabolism and gene expression. Previously, only the structure of rhodopsin, a GPCR member, was known. Reports from several laboratories elucidate the structure of β2-adrenergic receptors (β2ARs). The results are presented in a recent summary [34]. Both β2AR and rhodopsin are made up of a protein chain that passes through the cell membrane seven times. Some GPCR agonists elicit higher levels of activity than others, which may reflect different binding modes. The various interactions appear to be related to triggers present in the GPCRs. One example is an ionic lock comprising electrostatic interaction between a triad of charged amino acids.

Distance is an important variable in relation to electrostatic effects. Activity of β2AR is evidently related to structural rearrangement involving conformational changes [34]. Alteration in electrostatic forces by movement of protein chains may be a factor. The report of electrostatic involvement in GPCR activity provides support for our prior proposal [2–4] suggesting importance of such a factor.

8. The Hofmeister effect

Beginning in the late 1880s, Hofmeister found that ions have various effects on solution properties, such as protein precipitation and unfolding, as well as surface tension [35]. Many of the reasons for the influences that were proposed over the years have been called into question or shown to be incorrect. The ionic effects follow a “mysterious order”: for anions, sulfate > phosphate > chloride > nitrate > nitrite > chloride > iodide > perchlorate > thiocyanate; and for cations, ammonium > potassium > calcium > lithium > magnesium > sodium > chloride > nitrate > chloride > iodide > perchlorate > thiocyanate. It is intriguing that elements of the order are in accord with effects of these in receptors and cell signaling [2–4]. For example, phosphate and sulfate, particularly phosphate, are important actors in cell signaling. In relation to receptor interaction and signal transduction, a number of the more prominent cations, e.g. acetylcholine, GABA zwitterion and zwitterions of z-amino acids, such as glutamic, are organic analogs of the ammonium ion. Of particular interest is a recent mechanistic proposal [36]. Studies show that the effects of ions on the spectra of OH vibrations in water can be attributed to the electric fields of the ions acting on neighboring molecules, not to the long range effects on bulk water structure as previously hypothesized. Electrostatic potential energy decays less rapidly with distance than with the field strength itself. Hence, the electrostatic approach represents a unifying thread.

9. Conclusion

This review provides evidence for pervasive participation of electrostatics in biosystems, including both animal and plant. Focus is on the involvement of energetics in a variety of systems, apparently related to molecular electrostatic potential, which is stronger for ions in comparison with dipoles. Distance is an important factor in the operation of these forces. Hence, bioelectrostatics can be regarded as a significant unifying theme in biochemistry. Unfortunately, this area has been neglected, partly due to the lack of knowledge and difficulty associated with bioelectrical phenomena. More research is needed, especially involving interdisciplinary.

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References