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Electroceuticals: emerging applications beyond the nervous system and excitable tissues

Swarnalatha Balasubramanian,[1] David A. Weston,[2] Michael Levin,[3,4] and Devon Charles Cardoso Davidian[3,*]

Electroceuticals have evolved beyond devices manipulating neuronal signaling for symptomatic treatment, becoming more precise and disease modulating and expanding beyond the nervous system. These advancements promise transformative applications in arthritis, cancer treatment, tissue regeneration, and more. Here, we discuss these recent advances and offer insights for future research.

Application of electroceuticals is expanding beyond the nervous system

The nervous system has a central role in controlling functional and homeostatic processes in the body through system-wide communication via electric impulses. Directly manipulating neuronal signaling using electric pulses and targeting bioelectric properties of relevant nonexcitable cells in body tissues with ion channel drugs have emerged recently as a novel class of treatment called **electroceuticals** (see Glossary). Despite their high therapeutic potential, strong initial industry interest, and major initiatives from the US government (National Institutes of Health Stimulating Peripheral Activity to Relieve Conditions and Defense Advanced Research Projects Agency Electrical Prescriptions), electroceuticals have only begun to be explored [1]. However, with many devices in clinical trials and new research delving into the interplay between electroceuticals and **bioelectricity**, the field is poised to make a significant impact in not just neurological disorders but also inflammation, cancer, and regeneration [2–4]. We discuss the evolution of electroceuticals in the past decade to inform future directions.

Electroceuticals are becoming precise and disease modulating

'Electroceuticals', a portmanteau of 'electronic' and 'pharmaceuticals', was coined over a decade ago to describe the manipulation of neuronal signaling using devices for therapeutic effect [1]. Since their initial description, the sophistication and application of electroceuticals have deepened and widened respectively, providing an emerging ecosystem of interventions to target a wide range of diseases [5]. The first generation of electroceuticals cover a set of established therapeutic interventions, such as pacemakers, cardiac defibrillators, cochlear and retinal implants, transcutaneous electrical nerve stimulation, spinal cord stimulation, and deep brain stimulation, that utilize electric current to cause an effect (Figure 1) [5,6]. While undoubtedly clinically successful, these interventions are relatively broad acting and target excitable tissues (as opposed to individual nerve fibers or bundles) [6]. They use simple waveforms that are not calibrated based on the mechanism of action and mediate symptoms in a nonspecific manner without full understanding of the underlying biological effect [6].

The second generation of electroceuticals aims for a more targeted electromodulation for disease modification. This includes utilizing miniaturized devices that target a subset of nerve fibers or bundles, underpinned by a more thorough mechanistic understanding of biology [2]. The clinical trials of these devices align more closely to pharmaceutical drug development, with the scope extending beyond neurological disorders (Figure 1) [2]. SetPoint's MicroRegulator system [2] and Galvani's splenic stimulation system [7] are good examples of this category. Although **vagus nerve** stimulation (VNS) has been around for more than 30 years, and some of the VNS devices (such as transcutaneous vagus nerve stimulators) would be considered first generation, these two devices target the vagus nerve with increasing precision and are built on a deeper understanding of the neural–molecular–inflammatory pathways [2,7]. They stem from pioneering work by Kevin Tracey and Paul Peter Tak who characterized the vagal inflammatory reflex, providing the first demonstration that the nervous system reflexively regulates the inflammatory response in real time [8]. Genovese *et al*. followed this observation in a sham-controlled study and showed that

Glossary

Bioelectricity: refers to endogenous electric signaling that occurs in every cell (not just nerves and muscles) via flow of charged ions and molecules across their insulated membranes through ion channels, pumps, and gap junctions. In the organism, these signaling processes create bioelectric circuits directing individual cell behaviors toward specific anatomical endpoints. Bioelectric signaling can be delineated from biochemical signaling by the fact that the sensing machinery of the cells receiving the signal is specifically responding to the large-scale bioelectric state information, such as voltage or electric field, not local concentrations of specific ions. They are events that are initiated electrically rather than biochemically (e.g., changes in local electric fields leading to initiation of collective cellular migration).
Electroceuticals: a portmanteau of 'electronic' and 'pharmaceuticals'; traditionally describe the electrical manipulation of neuronal signaling using devices for therapeutic effect. Since its initial description, the concept has expanded beyond neurons and devices.
Electromics: large-scale measurement of bioelectric signaling within cells, tissues, and organs in healthy and diseased physiologic states.
Faradaic currents: produced by the movement of electrons between electrochemical mediators during redox reactions in cells.
Vagus nerve: tenth cranial nerve extending from the brainstem to the abdomen. The vagus nerve is a main component of the parasympathetic nervous system. It regulates key bodily functions, such as digestion, heart rate, mood, and immune response and plays a vital role in the gut–brain axis.

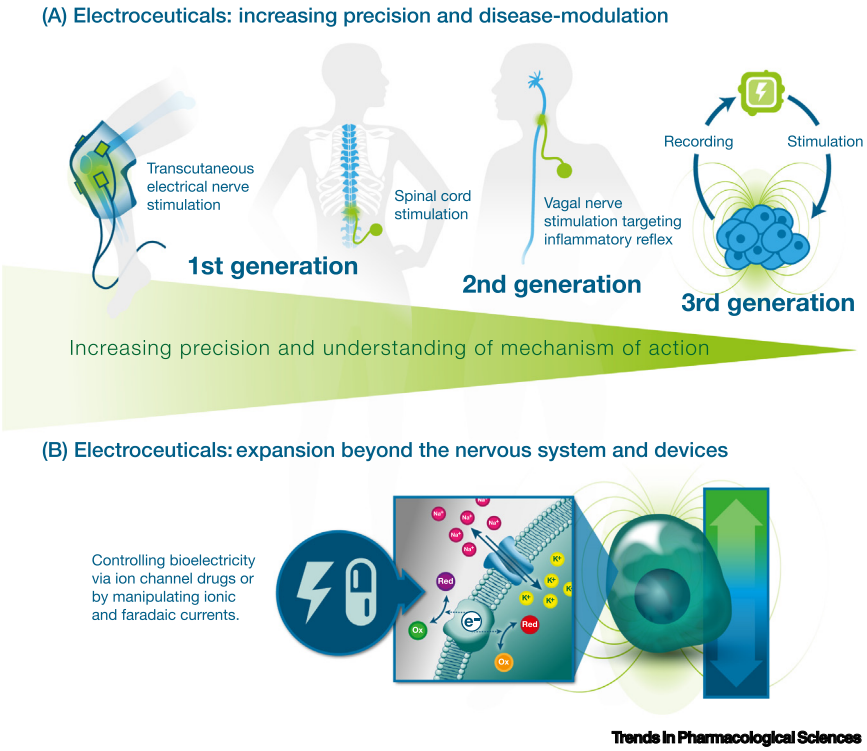

Figure 1. Evolution of electroceuticals. Over time, electroceuticals have evolved to become more precise and disease modulating and expand beyond the nervous system. (A) The first generation of electroceuticals cover a set of established therapeutic interventions, such as transcutaneous electrical nerve stimulation and spinal cord stimulation, and are broad acting, target excitable tissues, mediate symptoms, and utilize electric current to cause an effect [6]. The second generation of electroceuticals are able to target difficult-to-treat diseases with greater precision by stimulating the body's natural biological responses, like those designed to specifically target the vagal inflammatory reflex [2]. We envision the third generation of electroceuticals to be even more precise, specifically mechanism-based targeting of certain nerve fibers or individual cells [5]. (B) Electroceuticals expand the concept beyond the nervous system and excitable tissues to a much wider set of cell types and tissues and use drugs or devices to modulate bioelectricity at the cellular level [3,15]. All panels by Jeremy Guay of Peregrine Creative.

VNS is safe and well tolerated and improves symptoms in multidrug refractory rheumatoid arthritis (RA) patients [2]. This hypothesis on the vagal inflammatory reflex is now being further evaluated in larger patient cohorts in SetPoint's RESET-RA clinical study [2] and Galvani's splenic stimulation study [1]. Both of these trials aim to treat multidrug refractory RA patients by electrically stimulating the vagus nerve but at different locations. In the RESET-RA trial, the vagus nerve is stimulated through a small device implanted in the side of the neck. The preset stimulation schedule of 1 min per day is intended to maximize the therapeutic effect over side effects. The Galvani trial stimulates the splenic nerve and gets more precise and closer to the target organ, with the hopes of further reducing off-target effects. While we use generational classification to demarcate major advances in the field, the devices exist on a continuum in terms of their ability to precisely affect target pathways.

Some of the key unknowns here are that we do not yet know how big of a mechanistic treatment effect size we can expect from these devices, the optimal therapeutic window for dosing, and the level of precision needed (targeting individual nerve fibers vs. nerve bundles) to avoid undesirable side effects. This is complicated by the lack of clinical biomarkers for optimizing electric dosing and stratifying patients based on the likelihood of treatment response [9]. However, development of new methods to guide therapy, such as neural and non-neural biomarkers and closed loop and synchronized electrical stimulation, is now underway to address some of these challenges [5,10]. Looking forward, it is hoped that if sufficiently powered clinical studies of these second-generation devices are favorable, this will provide much-needed clinical validation.

Electroceuticals are expanding beyond the nervous system and target the endogenous bioelectric signaling present in every cell

It is increasingly realized [11,12] that the relevance of electroceuticals extends far beyond the nervous system and excitable tissues to a much wider set of cell types and organs, bringing forth potential for intervention in areas as diverse as oncology, birth defects, regenerative medicine, and metabolic disease (Figure 1). Electroceuticals leverage fundamental bioelectric properties of tissues first observed by Harold Saxton Burr and Elmer J. Lund, who recorded bioelectric phenomena such as changing electrical potential in developing chick and amphibian embryos and temporal changes in the wounds of guinea pigs [12]. This laid the foundation for our understanding that endogenous bioelectric signaling via resting potentials of all cell types ('developmental bioelectricity') is a powerful interface to exert system-level controls of form and function [12]. The molecular components (ion channel and gap junction proteins) of the networks by which groups of cells process information are ancient and predate the evolution of nerves and muscles. The nature of the bioelectric control system is evidenced in mechanisms enabling cells during embryogenesis to know what structures to build, when to stop, and how to repair it when processes go wrong, with bioelectricity deeply intertwined in the dogma of cellular information processing [11,12]. Thus, the bioelectric control mechanisms present in

every tissue in the body are a powerful, ubiquitous interface for reprogramming the software of life. This control can be achieved via manipulating ionic or **faradaic currents** in the cell using electrode- or drug-based electroceuticals. This has major implications not only for addressing diseases of structure and function but also for novel efforts in animal and plant bioengineering.

At a cellular level, bioelectric properties, such as depolarized resting potential and reduced bioelectric coupling, in individual cells and cell groups precede and actively regulate the onset of cancer [13]. Learning to decode steady-state and time-dependent [14] bioelectric signaling within tumors and between tumor and healthy tissue is an exciting emerging field for diagnostics and beyond. Manipulation of endogenous electric signaling can mitigate cancer, normalize tumor growth, and impede metastasis [15,16]. In wounds, the transepithelial membrane potential assumes a more negative charge at the site of the wound (depolarized) than at the unwounded epidermis, creating an electrical gradient that directs cell migration into the wound, a process known as electrotaxis [17]. This principle has inspired the development of electroceutical dressings that promote and even enhance the wound healing process [17]. Other applications in lower animal models have used optogenetic, chemical, and molecular electroceuticals to rectify genetic or chemical birth defects (targeting the brain, gut, and heart), induce appendage regeneration, and form complex organs (such as the eye) with simple bioelectric patterns induced by ion channel mRNA or ion channel drugs [11]. These interventions can now be rationally inferred by bioelectric simulator platforms that are starting to come online [4]. All of this together demonstrates that bioelectric information processing is a tractable target with which to guide the formation and patterning of complex native and bioengineered constructs from individual components.

As with traditional electrode-based electroceuticals, the wider field of developmental bioelectricity is also progressing from first-generation treatments such as ion channel drugs that depolarize or hyperpolarize cells. Second-generation treatments, like hyperpolarization-activated cyclic nucleotide-gated potassium and sodium channel 2 modulators, target context-sensitive ion channels that enable differential bioelectric effects in different tissues, providing repair functionality to complex organs such as the developing brain, removing the need for targeted drug delivery [4]. An example of third-generation treatments is an engineered smart controller (either an implant or wearable device) that will leverage the native property of cell and tissue bioelectrics to decode disease-state information, recognize the

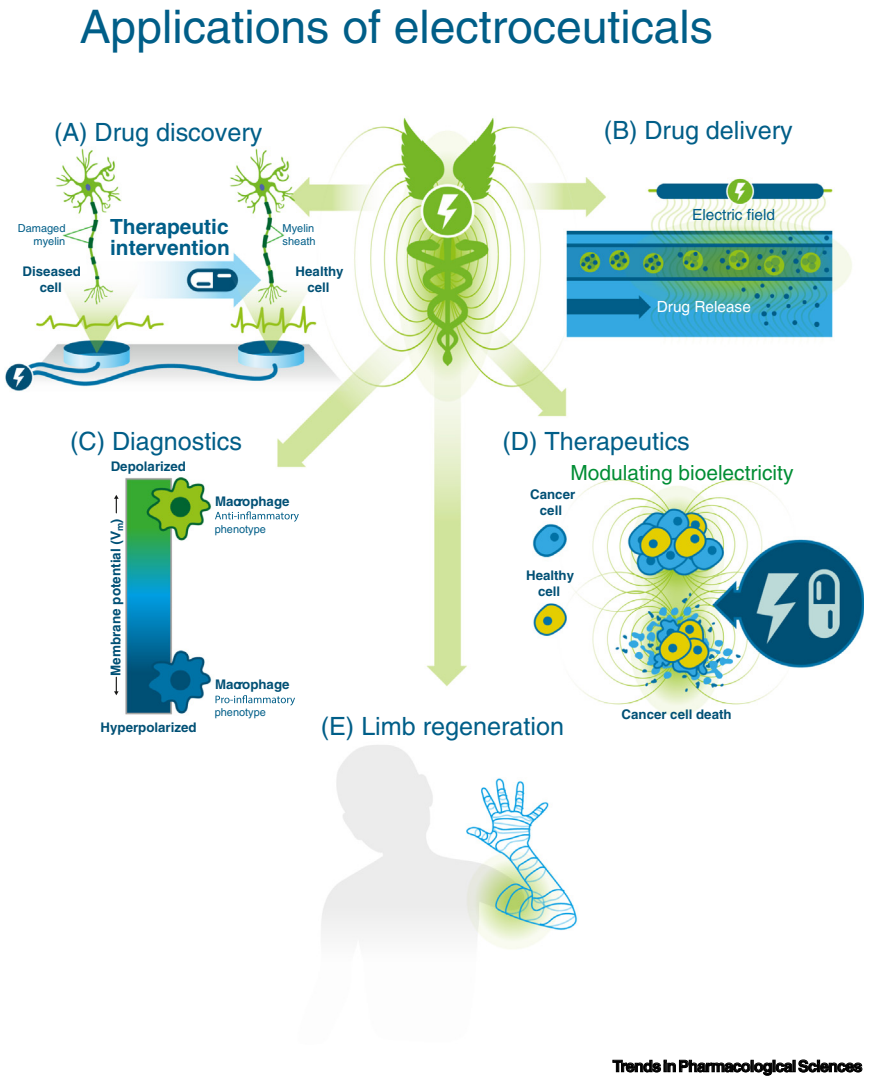

Figure 2. Applications of electroceuticals. The principles of electroceuticals could be applied toward (A) drug discovery, for example, by measuring the effectiveness of a therapeutic intervention using the bioelectric signature of cells [21], (B) drug delivery by electrically controlling spatiotemporal targeted delivery of gene therapies [22], (C) diagnostics by noninvasively diagnosing diseases [20], (D) therapeutics by treating diseases such as cancer by manipulating bioelectricity using ion channel drugs [3,15], and (E) limb regeneration by instating correct bioelectric patterns into tissue [12]. All panels by Jeremy Guay of Peregrine Creative. Panel (C) adapted from [20].

onset of disease, and impose a revised bioelectric state to intervene and pre-emptively resolve the disease [18]. A key current limitation of this approach is that the full range of the repair capabilities that can be controlled via the bioelectric interface is still being characterized.

Concluding remarks

One of the most significant discoveries in this field over the past decade has been that the tools and profound insights of neuroscience extend beyond neurons to many different cell types and contexts throughout the body [19]. We see several initial research efforts along these lines, including in the precise treatment of diseases by reading and writing the body's electric data in real time [5], noninvasively diagnosing diseases [20], and measuring the effectiveness of a therapeutic intervention using the bioelectric signature of cells [21]; promotion of limb and organ regeneration by instating correct bioelectric pattern memories into tissue [12]; use of **electromic** datasets to guide drug development [21]; and electrical control of spatiotemporal targeted delivery of gene therapies [22] (Figure 2). To translate these research concepts from the laboratory into tangible benefit for patients, we need more researchers focused on electroceuticals.

This increasing sophistication of electroceuticals represents a paradigm shift in therapeutic approaches and faces unique challenges from the standpoint of drug development. Therefore, to catalyze this field further, we call upon researchers to work toward (i) greater clarity around the native bioelectric code that specifies tissue- and organ-level structure, (ii) tools for better manipulation of neural- and nonneural bioelectric states in preclinical models and humans, (iii) exploration of the underlying mechanism by which cells respond to bioelectric signaling, (iv) encouragement of cross-collaboration between all players in the life science ecosystem to overcome the translational and clinical challenges that span cell biology, bioengineering, and computational neuroscience, and (v) a revised framework and development of terminologies that are inclusive of all branches of bioelectric research and therapies with the aim of bringing greater consistency to the field.

Declaration of interests

S.B. and D.A.W. are employees of AstraZeneca. M.L. is cofounder of a company (Morphoceuticals) which seeks to induce regenerative repair via bioelectric approaches. M.L. has research collaborations with Morphoceuticals and AstraZeneca.

[1]Emerging Innovations Unit, Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, Boston, Massachusetts, USA
[2]Emerging Innovations Unit, Discovery Sciences, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK
[3]Allen Discovery Center, Tufts University, Medford, MA, USA
[4]Wyss Institute, Harvard University, Boston, MA, USA

*Correspondence:
devon.davidian@tufts.edu (D.C.C. Davidian).

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