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Bioelectronic Medicines for Chronic Disease Management

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ABSTRACT

Bioelectronic medicines represent an innovative approach to chronic disease management by leveraging the peripheral nervous system's signaling mechanisms to modulate organ functions. These devices, known as electroceuticals, employ electrical impulses to interact with specific organs, offering a targeted and dynamic alternative to traditional pharmaceuticals. This paper explores the historical development, underlying principles, biological basis, and clinical applications of bioelectronic medicines. Focusing on neurological and metabolic disorders, we highlight recent advancements and clinical trials that demonstrate the potential of bioelectronic interventions to transform chronic disease treatment. The conclusion addresses the implications for healthcare, emphasizing the promise and challenges of integrating these technologies into standard medical practice.

Keywords: Bioelectronic medicines, Electroceuticals, Chronic disease management, Neuromodulation, Peripheral nervous system.

INTRODUCTION

Bioelectronic medicines leverage the mechanisms of signaling of the peripheral nervous system to modulate and control the functions of target organ systems. Bioelectronic medicine, or electroceuticals, may be defined as the clinical application of devices that communicate with the autonomic nervous system or the sensory nervous system, using electrical impulses or signals and algorithms to create an interface with the relevant organ or tissue. They are placed and operated in a more therapeutically targeted fashion than classical implantable devices are, frequently adopting stimulation rather than electrographic or electrophysiological recording of a condition. The use of a primary device processor differentiates bioelectronic medicine from less sophisticated timed stimulation devices used for therapeutic applications [1, 2]. The first direct electrical stimulation in medicine was initiated with the practice of electroconvulsive therapy in psychiatry more than 80 years ago in 1938. With the advent of the transistor in 1948, implantable devices and technologies came into being, with applications for neurological symptoms such as Parkinson's disease beginning in the 1960s. More recently, the field of spinal cord and peripheral nerve stimulation (SCS/PNS) devices has been growing as a major sector. The application of implanted stimulatory devices in non-central or peripheral nervous system targets, branching out into non-thoracic and non-ventral rhizotomies and epidural SCS/PNS, has been increasing year-on-year and aged with the staff and expertise in these technologies [3].

DEFINITION AND PRINCIPLES

Bioelectronic medicines denote a new generation of therapeutic agents that modulate the detected aberrant peripheral electrical activity at visceral target organs, owing to chronic disease processes, disrupted homeostasis, and dysfunctional organ actions. The term bioelectronic medicine has further been used to describe a new healthcare model focused on using approaches developed within the bioelectronics field to better understand and diagnose disease states and to inform and improve therapeutic interventions. This article is focused solely on the development and mechanism of potential action of bioelectronic medicine. Bioelectronic medicines for treating visceral disorders are characterized with respect to their potential action, starting with detection strategies to differentiate between the healthy state and an established aberrant disease-related situation, which provides validation and feasibility of use-relevancy for the treatment of long-term (chronic), rather than acute, disorders [4]. Bioelectronics forms part of the wider field aimed at delivering neuromodulation/stimulation of fine conducting nerves, related to the control of a specifically targeted viscera and its organ functions. Implantable pacemakers and other neurostimulators have been increasingly developed at an ever-faster pace after the mid-20th century. What is of particular and central importance to our definition of bioelectronic medicine is its integration within the time-varying, ever-changing physiological processes of health and disease. There are four underlying principles for bioelectronic medicine. First, its development should rely on the detection and quantification of the characteristic patterns of electrical signaling related to active disease processes, in comparison to integrated regular physiological operational continuous action which is normative of the organism as a whole [5].

HISTORICAL BACKGROUND

Bioelectronic medicine (a.k.a. electroceuticals) is a relatively new field in medicine that attempts to treat chronic diseases through the modulation of the peripheral nervous system and hence provide electronic substitutes for pharmaceuticals. It was recently warranted that the first bioelectronic device was implanted in 1965, releasing spinal cord stimulation surgical cords from paresthesias – long before PACEMAKER, also developed by Medtronic. Over 600,000 patients with arrhythmias and over a million Parkinson's patients worldwide have received the stimulator so far [6]. Staying in the same century, Galvani showed rejuvenation of dead Luigi Galvani muscles of frogs through contraction with externally applied electrical currents in 1791. Not only did Galvani's obstinacy with Alessandro Volta lead to the invention of the first battery that can provide a continuous direct current, but it also created a large platform that could facilitate the confluence of electrobiology. The electrochemical potential predicted by Volta is critical for the ionic denaturation to produce action potentials propagating along the axon, leading to electronic medical remediation through adjustable timing when the electrical engineering could produce high-frequency stimulator devices morse. This inspiring miniature version, designed by Jim Melker and associates of Medtronic, also Anne Vanhoestenberghe at Imperial College, mimics the Volta pile in the best way. Volta's confluence physiology reengineering remains an impressive modern version of Pacemakers that is becoming a fitting synthetic impulse as a single end substitute for robust medicinal rhythms [7, 8].

BIOLOGICAL BASIS OF BIOELECTRONIC MEDICINES

Neurological circuitry pervades the human body, forming a complex network of interconnected pathways that encode communication throughout the many tissues of the body. Hypertrade, showing regions with the highest percentage of inputs via a monosynaptic connection. Different tissues receive different neuro-input, and hence they respond differently to similar stimulations. As a result, it is increasingly acknowledged that treatments more targeted to the needs of individual patients are showing greater promise [9]. Bioelectronic Medicine, also termed electroceuticals, neuromodulation, has now moved center stage, allowing for interfacing with nerves that are driving inflammation in remote regions without the need for peripheral blood or neural concentration of agents such as antibodies, growth factors, molecularly engineered messenger RNA, post-transcriptional mRNA, siRNA encoding proteins/ defect correction cDNAs, specific drugs and/or gene-editing tools. Indeed, bioelectronic medicine is part of the wider field of electroceuticals and encompasses treatment of a range of diseases. Bioelectronics refers to electrical stimulation because the nervous system is at the forefront of both adhering to the dogma of 'organ-tissues-cells-genes-disease' back to the future homeostatic or 'it is all about electrophysiology' paradigms: eventually the ventral roots of the spinal cord that conduct efferents towards peripheral tissue will contain last lies/conite impulses. Subsequently, the efferent terminals in peripheral tissues will be the target for pharmacology or gene therapy and other tissue-based/organ-based remotely delivered agents that can be electroimmuno-stimulated nerves [10].

NEURAL CIRCUITRY AND COMMUNICATION

The human body is an intricately intertwined structure that communicates in numerous ways using a mix of synaptic and paracrine signals, diffusion of blood-borne factors, specialized regions of the brain, and cranial and peripheral nerves. For those nervous system-mediated signals, the basic unit of nervous tissue is the neuron. It is the building block of nervous systems and may communicate with other neurons, myocytes, or endocrine cells. A neuron consists of a cell body, dendrites, which transmit electrical signals from adjacent cells to the cell body, and an axon, which transmits the action potential away from the cell body to synapse onto an adjacent cell. When a neuron activates, an action potential travels down its axon to release neurotransmitters into the extracellular space between neurons or a synapse onto an end organ, like a skeletal muscle motor neuron, to permit rapid electrical transmission to disrupt a cell barrier in a process deemed exocytosis. These neurotransmitters interact with receptors of the subsequent cell either on adjacent membrane surfaces of cells or within gaps. Receptors undergo a conformational shift upon binding to the neurotransmitter or their respective ion channel, which causes the channel to open or close ions. The ions then flow through the channels, causing the respective cell to depolarize or hyperpolarize, which can also lead to the opening of additional channels or activation of signaling pathways. The summation of all of these events in the recipient cell provides the biological effect of the transmitter substance released by the topped cell and is critical in long-term potentiation and plasticity [11]. Only about one-tenth of the brain activity occurs through action potentials. Most electrical signaling involves subthreshold signal propagation through a specialized form of non-neural, nonmuscular, non-endocrine voracity called the action potential. An action potential is a transient depolarization of the membrane, which is also referred to as a nerve impulse or nerve signal. These are the signals that flow through the specialized cell called a neuron. Administered for short periods of time, they selectively halt the transmission of electrical signals between the stimulated neuron and the targeted nervous structure in a process known as conduction block. Neurons manage the external and internal environments of the human body, and external stimuli include a range of surface chemistries such as ultraviolet radiation, pheromones, and thermal changes. But among the key internal trigger signals are chronic changes in 47 physical and chemical energies within the host. Central cardiovascular regulation, the gastrointestinal tract for thirst and salt taste, pressure and luminal sensor systems, lactate or acid and glucose sensors, systemic inflammation antigens, breathing rhythm, and sensitivity to blood pressure are all kinds of receptors. These triggers provide some highly targetable feedback signals, and chronic disorders of all cause disruptions to these neural systems. At the base, the mechanisms of chronic diseases often share common properties like the central processing of homeostatic challenges. Bioelectronic medicine represents a form of neural-digital crossover by cutting out these cascaded amplifiers and going directly to the origin of the electrical communication in the body. Bioelectric medicine represents a form of neural-digital crossover by cutting out these cascaded amplifiers and going directly to the origin of the electrical communication in the body. Bioelectric targets range from homeostasis to neurotransmission of sterile inflammation. For example, the subdiaphragmatic vagus nerve transmits signals from the liver that instruct the brain to switch off the fibronectin production (a healing function) of the liver. A frayed vagus and her program, known as the Inflammatory Reflex or Cholinergic Anti-inflammatory Pathway, can be used to reduce inflammation and other essential conditions for squalling off the biological side effects of electronic fields [12, 13].

ROLE OF ELECTROCEUTICALS

Bioelectronic medicines have the potential to treat a range of diseases stemming from organ dysfunction that cannot be addressed or well managed with standard therapeutics. Because they are designed to intercept the neural information conduits that travel between the central nervous system (CNS) and target organs, bioelectronic interventions offer the potential to more directly modulate physiological pathways than pharmaceuticals. To date, most bioelectronic interventions to treat chronic disease have been in the form of small implants termed "neurostimulators", which work to modulate those neural information conduits to modulate organ function, with tremendous success in several different indications [14]. Bioengineers refer to the molecular targets and signaling pathways that can be modulated as "effectors". Because the central nervous system drives and modulates so many effectors, it is teeming with targets for therapeutic modulation. In this way, electrical signals and mediators in the form of neurotransmitters can be used to suppress hyperactivity of effectors causing disease, or alternatively to stimulate under-performing effectors. Electroceuticals work in a different way, namely, they are used to measure specific biological signals emanating from the body, or can be used to deliver small molecules or peptides, like those being tested in clinical trials by the Stanford bioelectric engineering group. Thus, electroceuticals make it possible to measure or deliver (on-demand) factors and therefore treat conditions where the primary pathophysiology is not driven by the autonomic nervous system itself [15].

APPLICATIONS IN CHRONIC DISEASE MANAGEMENT

Bioelectronic medicines, also called electroceuticals, are innovative devices that expertly detect and/or modulate specific elements of the peripheral nervous system with the potential to treat a wide range of chronic diseases. Bioelectronic medicines work by directly modulating the electrical signals within the nervous system and, by doing so, also achieving control of disease pathways. Coined as the third technological advancement in modern medicine in the 21st century, following the advent of biologics and gene therapy, bioelectronic medicines are an emerging preclinical and clinical field where combined human physiology and electrical engineering are put to use to design and conduct projects that could revolutionize the way we treat chronic diseases [16]. Chronic diseases can be modified by engineering the spleen (e.g., inflammatory disease of metabolic etiologies), by interfacing with the somatic nervous system (e.g., metabolic disease of adipose tissue), muscle (e.g., glycemic control by the skeletal muscle), and associated muscle organs (e.g., visceral autonomic reflex of the lower esophageal sphincter). For example, activation of the spleen can train bone marrow to produce more regulatory T cells that can control inflammation in many tissues, presenting a novel therapeutic option for a wide array of chronic diseases affected by inflammation. Metabolic disease can be modulated by targeting the dorsal root ganglia, adipose tissue, liver, pancreas, and skeletal muscle nerves to treat various morbidities associated with obesity. Brain interface work is poised to control many symptoms mediated by the brain (e.g., depression, anxiety, and panic attack) and reversible psychiatric disease (e.g., Alzheimer's and bipolar disorder). It will be important to discover if any of these devices can be effective long-term treatment [17].

NEUROLOGICAL DISORDERS

The practice of bioelectronic medicine is well-suited for diseases that are related to the nervous system and its control over the internal functions of the human body, such as metabolic regulation. Neurological disorders, such as headaches, pain syndromes, epilepsy, depression, and abnormal behaviors, have been the focus of some of the early and ongoing trials of such bioelectronic devices. The disadvantage of bioelectric medicine is that it is usually slow-acting (requiring a few weeks to take effect with months necessary for full efficacy), may lose effect over time, and may not be suitable for the delivery of stimulus fields and patterns that may provide the best long-term benefits, such as signals that may provide continual suppression of synaptic signaling within a specific pathway [2]. The development of bioelectric approaches, such as transcranial magnetic stimulation to alleviate migraine and depression and implanted VNS devices developed to control seizures and depression, may be able to address part or all of the limitations by using re-entrant nerve pathways to access the central nervous system and provide signals similar to endogenously-evoked pathways. Hence, through use of the emerging bioactive-electronics platforms, rather than providing a buffer solution or media, artificial tissue devices may be capable of providing reassortment of signals to work in tandem with the intact circuitry of a specific neural pathway through these choreographed interactions. Furthermore, bioelectric therapies may be more efficient than established pharmaceuticals, given the specificity. Bioelectric devices can provide feedback, monitoring patient status and fine-tuning the signals as disorders naturally evolve in an individual. The possibility of close-loop operation positions bioelectric medicines as prime candidates for early chronic disease management [10].

METABOLIC DISEASES

A broad area of disease category for bioelectronic medicine covers metabolism, associated with storage and expenditure of the energy used by the body's cell functions. Management of metabolic disease involves mostly lifestyle changes or medications, like diet management, lifestyle modification, medication by tablets or injectables together with numerous possibilities for active implanted therapy; for example, intragastric balloon, endobarrier gastrointestinal liner, endosleeve, and vagus nerve (VN) stimulation, and recently established liver neurostimulator. All those embedded treatments individually or as combined bariatric techniques are much effective in treating diabetes, obesity, and cardiovascular risk. Bioelectronic medicine is a unique technique for the management of metabolic diseases through modulation of electrical impulses present inside the body. At the cellular level in the pancreas, alteration in membrane voltage or calcium homeostasis or ion channels present inside the beta cells showed relationship with secreting insulin when variety of substances like glucose, hormones, and neurotransmitters may interact with beta cells, thus modulate insulin secretion. Metabolism mainly involves two types of bioelectronic-based treatment strategies, i.e., either neuro-augmenting or gastric pacemaker [1]. Bariatric surgery, like PRAGUE-9 P-ORBIT, showed that significant hypotensions from 30/42 participants (64%) were observed after the laparoscopic VBLOC therapy, which reduced inflammation, lipid, and insulin levels, and significant weight loss with loss of fat mass when applied single. Bioelectric physiology thus has potential to cause electrical interactions by blood glucose level on the pancreas' alpha and beta cells can hence directly help in reducing secretion of glucagon and release of insulin acting specifically the pancreatic output. VNS on splanchnic nerve stimulation may block the pancreatic exocrine secretion. Extensive studies using pigs and dogs using the VBLOC system showed about 86% of reduction in motility measured by reduction in electromyography in proximal or distal stomach and approximately 40% reduction of food intake and weight loss 20% until 29 weeks. More and more studies are presently carried out using laparoscopic implants of VBLOC in human patients using a rechargeable implant. One-year follow-up of laparoscopically implanted VBLOC, maintain good safety and tolerance of the device, thereby controlling hemorrhage, abscess, perforation, or any device-related death. It works on BMI 30 and 70 of 294 participants starting from 1 year and trend maintained up to 6 years was decline in BMI was up to 10-15%. Just like VBLOC, several alternative devices were suggested; for example, Maestro implantable gastric stimulation, with two pulse generators powered from externally renewed transcutaneous transmitter, made of 48-electrode lead to contact to the anterior and posterior abdominal vagal trunks, and so on. These previous few studies may actually expand vision, that bioelectronics treatment alternatives for managing metabolic health in human remains broad [18].

CLINICAL TRIALS AND FUTURE DIRECTIONS

Pivotal to the bioelectronic medicine sector is the successful ideation, execution, and monitoring of clinical trials. To assist in this process, The Feinstein Institutes for Medical Research (23-5-0928) hosts, which houses a comprehensive and complete list of clinical trials within the bioelectronic medicine domain. The information provided includes a summary of clinical trials, description of study designs, information about the participants and recruitment plans, and the expected outcomes for the listed area(s) of focus. Additionally, each listed clinical trial contains links to more information and to the recruitment page of ClinicalTrials.gov. The experience of the pre-clinical testing in animal models and then the translation into clinical settings most often requires a shift in electrode design due to anatomy. There are several electrode detectors currently in clinical trial [19]. Ideas for future directions for reflex-based bioelectronic medicine are many, and many are blue-sky thinking. Ideally, the approach, given the highly invasive method, will be limited to individuals in wheelchairs, and a method is identified where this treatment can be administered at home. To understand other potential areas of research activity, present symptomatic treatments involve electrical stimulation (deep brain, sacral nerve, and paresthesia spinal cord stimulation) or drugs (including triptans, used acutely, and four options of preventive drugs). The objective is to artificially induce the patterns based on the natural regulation of the sympathetic nervous system using implantable devices in a small number of individuals living with chronic intractable migraine headaches. By successfully reducing or eliminating the number of migraine headache days, individuals can come off the medications with potentially significant lifestyle improvement [20].

IMPLICATIONS FOR HEALTHCARE

Chronic diseases pose substantial pressures to individuals, healthcare systems, and society. They require continuous, individualized care that is not always possible due to the variations in patient responses to pharmacological treatment. Although some individuals respond well, there are many others who are resistant to standard medications or whose conditions worsen over time. The use of electronic devices has made it possible to develop bioelectronic medicines. These technologies sense biological signals and apply an electronic input to alter organ function according to the specific need of one patient. The vagus nerve is the most popular organ of interest due to modulatory inflammatory responses in clinical trials [21, 22]. The development of bioelectronic treatment modalities is currently being explored by two major companies who are using slight variations of VNS, and several academic labs have reported experimental successes in VNS for a variety of pathology. Although this innovative approach has considerable potential, further research in patients and research participants will be needed to fully assess the broader applicability and potential risks and drawbacks. In addition, improved delivery systems for these kinds of therapies could also maximize the degree of therapeutic improvement. These extraordinary inventive drugs, when combined with state-of-the-art treatment principles and a proper combination of medication and interventions, are forecast to change the way in which patients with chronic illness are managed for the coming years. With a pre-emptive combination of intervention and medication in the acute to borderline situation, the strategy of prevention and cure is progressing. Bioelectronic medicines can also contribute to individualizing care, reducing the expense of "trial and error" medication, and enhancing the efficacy and speed of medical treatment adjustments [1].

CONCLUSION

Bioelectronic medicines offer a groundbreaking avenue for managing chronic diseases by directly modulating electrical signals within the peripheral nervous system. These innovative devices hold the potential to revolutionize treatment paradigms for conditions such as neurological and metabolic disorders, providing targeted, adaptive, and often more effective alternatives to conventional pharmaceuticals. As clinical trials continue to validate their efficacy and safety, bioelectronic medicines are poised to become a pivotal component of personalized medicine. However, challenges remain, including the need for further research to optimize device design and functionality, as well as to address long-term safety and efficacy. The integration of bioelectronic medicines into healthcare systems could significantly enhance treatment outcomes, reduce costs associated with trial-and-error medication approaches, and ultimately improve the quality of life for patients with chronic conditions.

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