IJPSR (2020), Volume 11, Issue 9 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 15 December 2019; received in revised form, 25 March 2020; accepted, 30 March 2020; published 01 September 2020

BIOELECTRONIC MEDICINES: INNOVATION IN DISEASE TREATMENT

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Keywords:

Bioelectronic medicine, Electrical signaling patterns, Nervous system, Diseases

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ABSTRACT: Innovation in technology is required to change the world. Bioelectronic medicine is the consolidation of molecular medicine, neuroscience, engineering, and computing to develop a device to diagnose and treat diseases. The mechanisms of Bioelectronic medicine for neural control of a biological process that underlie disease and the development of devices to modulate these specific neural circuits as therapy using electrons instead of drugs. Bioelectronic medicine has emerged at a convergent epicenter in health care, technology, and science. Bioelectronic medicine is a new way to treat disease. Today patients are treated by either drug, which can lead to a side effect or drive up costs, which can mask pain signals but they usually can't mask the central cause of disease. With the rapid rise in technology for the precision detection & modulation of electrical signaling patterns in the nervous system is a new class of treatment known as bioelectronic medicines. Specifically, the peripheral nervous system will be at the center of this advance, as the functions it controls in chronic disease are extensive. The vision for bioelectronic medicine is one of the tiny, implantable devices that can be attached to individual peripheral nerves. Such devices will be able to decipher & modulate neural signaling patterns, achieving therapeutic effects that are targeted at signal function of a specific organ. This new field was exploring the potential to treat Paralysis, Diabetes, Rheumatoid arthritis, chronic disease, Hypertension, blind diseases *etc*.

INTRODUCTION: Bioelectronic medicine is devices that use electricity to regulate biological processes, treat diseases, or restore lost functionality. BEMS can interact with excitable tissue in 3 distinct manners: they can induce, block & sense electrical activity. Specifically, the peripheral nervous system will be at the center of this advance, as the function it controls in chronic disease is extensive.

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DOI: 10.13040/IJPSR.0975-8232.11(9).4229-37

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(9).4229-37

The vision for bioelectronic medicines is one of the nano, implantable devices that can be attached to individual peripheral nerves. Such devices will be able to decipher & modulate neural signaling patterns, achieving a therapeutic effect that is targeted at the signal function of a specific organ. The bioelectronic field has been able to move forward recently with the development of more complex devices and novel materials that have been engineered down to the nanoscale.

These revolutionary breakthroughs in our ability to miniaturize device components create flexible and biocompatible materials and design more efficient and expandable components for computation and power, which reduce the side-effects, miniatu-rization, and cost reduction. BEms need to target various sites in the human body and operate in a closed-loop manner [1, 2]. Bioelectronic devices can already be found in many applications in the medical sector. Indeed, electronic medical devices are now a mature technology. Examples include deep-brain stimulations to treat Parkinson's disease [3], neural stimulation to treat epilepsy or paralysis [4], cochlear and vestibular implants for hearing and balance [5, 6,] and retinal prosthetic devices to treat blindness or vision loss [7, 8]. The human urinary tract is complex and sophisticated; it includes our kidneys, ureters, bladder, and urethra, and its natural control mechanisms pass through both the central as well as the peripheral nervous system (PNS). Restoration of full control of the urinary tract could, therefore, be possible *via* a variety of approaches; some of those could require a distributed wireless system of BEMs, in which each unit is responsible for specific functionality, but all are communicating and working together in a coordinated fashion to deliver the required therapy. The potential of this new field of medicine to be precise than drugs at reaching their targets. The main problem with drugs is that they not only treat diseased cells but also go everywhere else in the body. Even the best drugs have a side effect on other organs [9, 10].

If bioelectronics technology enables real-time monitoring of treatment adherence and effectiveness, the impact on mortality and morbidity outcomes could be profound. Bioelectronic devices are also used in the central nervous system [11, 12].

Novel methods in machine learning, symbolic reasoning, and signal processing are under development to improve the deconvolution of the electrical activity in both the central and peripheral nervous systems. Progress in the new field of bioelectronic medicine and underlying neurophysiological and molecular mechanisms make it possible to target specific circuits to treat disease and improve organ function [13]. That prospect certainly promises a significant leap forward in both treatment efficacy and safety, based upon utilizing electrons to replace drugs [14].

Components of Bioelectronic: In bioelectronic medicine, interfaces are required to access the peripheral nerves, which are listed below, and some are shown in **Fig. 1.**

- **Electrode:** Silicone based penetrating electrode [15, 16], polymer based fine, time, life & cuff electrode arrays [17, 18], Complementary metal oxide semiconductor.
- **Material:** Noble metal, Alloys, Platinum, Platinum- iridium, Gold, Laser patterned
- Gold or Platinum iridium foil (12 micrometer), lithographically patterned gold or Platinumthin (300 nm), Films on polyamide or polylene, thermally evaporated Ultra Thin (35 nm)
- **Polymer:** Polyimide [19-22], parylene [23-25], polydimethyl siloxane (PDMS) [26-28], liquid Crystal polymer [29-30], SU-8 photoresist [31, 32], polyurethane [33], Sheet or film (polyimide).
- **Light:** Emitting diodes for optogenetic stimulation, receiving elements for wireless Power transfer, such as inductors, antenns and ultrasonic transducer.

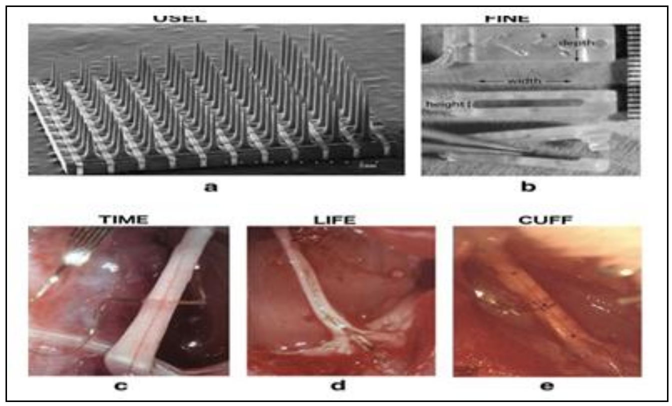

FIG. 1: COMPONENT OF BIOELECTRONIC

Mechanism of Bioelectronic Medicine: All body organ functions are regulated through neural circuits communicating by electrical impulses; it should theoretically be possible to interpret the electrical language of diseases. By extension, it could be possible to stimulate or inhibit the malfunctioning pathways with tiny electrodes in order to correct the defect. This micromanipulation of the nervous system targeting impulses(action potentials) to specific cells within neural circuits could conceivably be exploited to manipulate abroad range of bodily functions, such as controlling appetite or blood pressure or stimulating the release of insulin in response to rising blood sugar, Strategy to isolate the nerve bundles sending efferent signals involved in specific diseases from the peripheral nervous system to the brain, and blocking them will likely involve an invasive procedure [34, 35]. BEMs help includes: 1) Understanding molecule/cell-electronic Interfaces. 2) Understanding cellular responses and the variabilities to stimulation (electrical, mechanical, chemical, thermal, and the like). 3) Ability to collect and analyze essential data on the state of bimolecular and cells (chemical, physical, structural, functional). 3) Ability to monitor, in real-time, the biochemistry of a single cell or a population of cells, which requires comprehension of interaction between molecules. Ability to deliver appropriate therapeutic materials and stimuli in real-time; and ability to detect, identify and quantify thousands of different biomarkers simultaneously [36]. The vagus nerve, which connects the brainstem to several organ systems in the body, has a putative connection with the splenic nerve, part of the sympathetic nervous system. It is through this connection that a technique called vagal-nerve stimulation is thought to reduce inflammation, which is shown in **Fig. 2**.

Current Researches in Bioelectronic Medicine:

1. Bioelectronic in Hypertension: Anti-hypertensive drug therapy is successful only to a point, leaving a significant percentage of patients nationwide with blood pressure measurements above guidelines despite being treated with at least three agents at maximally tolerated doses, consistent with a diagnosis of resistant hypertension [37]. The sympathetic nervous system is an effective homeostatic mechanism for modulating hemodynamic in times of stress and illness. Unfortunately, in some patients, this mechanism escapes physiologic control by carotid sinus, which is shown in **Fig. 3** and through various mechanisms lead to resistant hypertension [38, 39].

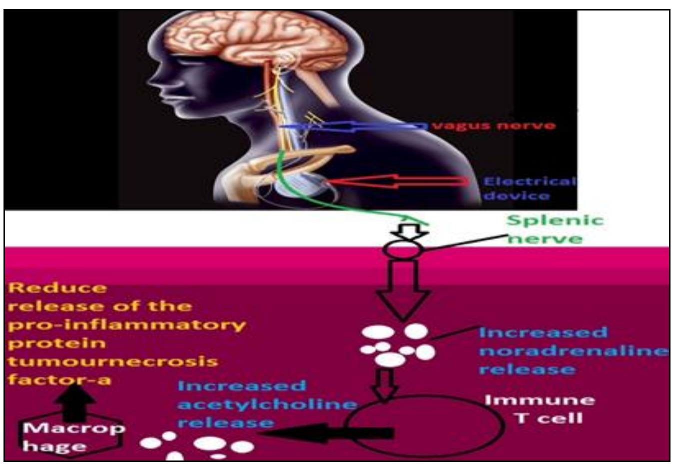

FIG. 2: MECHANISM OF BIOELECTRONIC MEDICINE

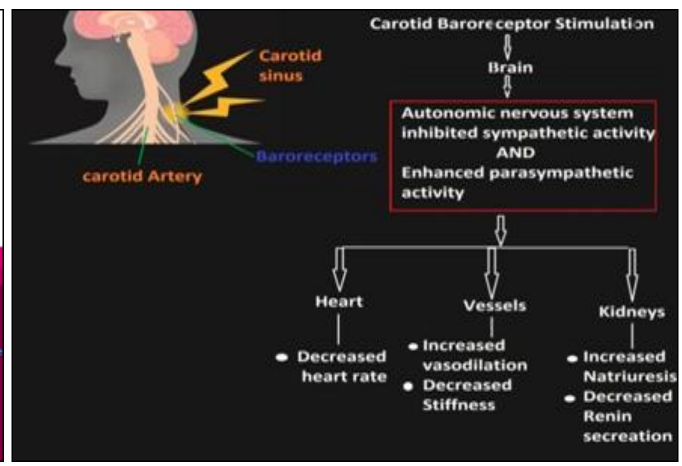

FIG. 3: BAROREFLEX ACTIVATION THERAPY IN HYPERTENSION

Baroreflex activation therapy in Hypertension, the system for delivering BAT (Barostim neo system, CVRx, Inc., Minneapolis, Minnesota) consists of a carotid sinus lead and a pulse generator [40]. The lead comprises a 40 -cm lead body that terminates in a circular backer 7 mm in diameter [41] with a ^{2}mm iridium oxide–coated platinum-iridium disk electrode centered on the backer [42, 43].

The pulse generator is implanted in the fashion of a pacemaker, by making a subcutaneous infraclavicular chest wall pocket to hold the pulse generator [44, 45]. Electrode implantation begins by surgically exposing the carotid sinus through a transverse cervical incision over the carotid bifurcation [46, 47]. Sensitivity is measured by observing hemodynamic changes associated with acute baroreflex activation, namely, reductions in heart rate and/or BP associated with increased parasympathetic traffic and / or decreased sympathetic traffic, respectively [48, 49]. With the correct position identified, the electrode is directly affixed by applying 6 sutures [50], evenly spaced around the perimeter of the electrode backer through the backer and adventitia [51, 52].

The opposite end of the lead is brought to the pulse generator pocket by means of a subcutaneous tunnel and attached to the pulse generator. All incisions are then closed, and the procedure is complete [53, 54]. Therapy is initiated at a moderate level in the absence of side effects such as excessive reductions in heart rate or BP [55-57].

2. Bioelectronic in Rheumatoid Arthritis: Rheumatoid arthritis (RA) is a chronic autoimmune disease, which is characterized by pain, swelling, and stiffness of joints, due to synovial inflammation [58, 59]. During active disease, the joints are the persistence of synovial inflammation leads to the development of bone erosions and finally joint deformities [60, 61,] which is shown in **Fig. 4**. Bioelectronic medicine is increasingly becoming applied in clinical trials [62].

Patients suffering from rheumatoid arthritis that were implanted with a vagus nerve stimulator to activate the inflammatory reflex showed significant improvement of clinical signs and symptoms also in patients with previously therapy-resistant disease [63, 64]. Signals through the vagus are transduced through the nerve and trigger [65, 66]. Activation of inflammatory cells is reduced [67; 68]. This is reduced production of systemic inflammation mediators [69, 70]. Also, reduced activation of circulating immune cells decreased inflammation, decreased joint damage, and reduced joint pain [71,] which is shown in **Fig. 5.**

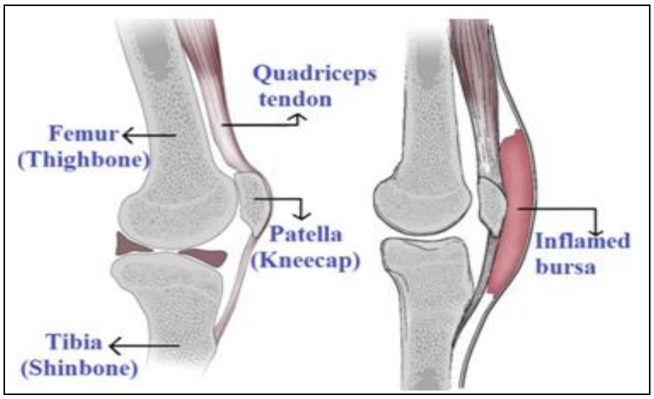

FIG. 4: BONE EROSIONS AND JOINT DEFORMITIES

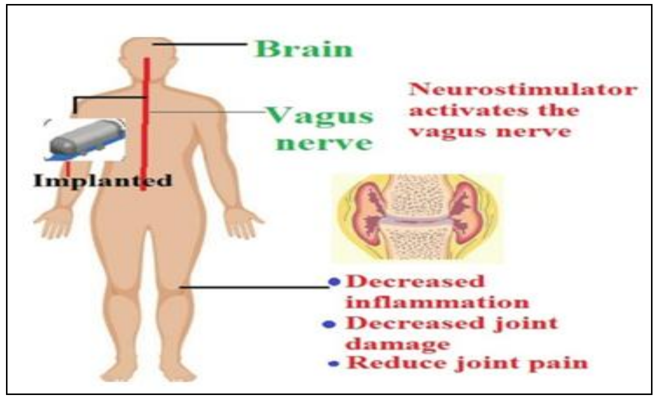

FIG. 5: BIOELECTRONIC IN RHEUMATOID ARTHRITIS

3. Bioelectronic in CNS Disease: VNS (vagus nerve stimulation) therapy has been approved as a treatment for epilepsy in Europe in 1994, and in the USin 1997 [72-73], in the US, VNS has also been approved for the treatment of depression [74, 75]. VNS can be performed after neurosurgical implantation of a vagus nerve stimulator; in 2012, 100,000 vagus nerve stimulators had been implanted [76, 77]. The device consists of two parts: a pulse generator and a lead with electrodes. The pulse generator contains the battery and the stimulation system [78] and is positioned subcutaneously below the left clavicle on the pectoral muscle [79]. It is connected to the left vagus nerve in the neck via the lead, with three helices at the end: one positive electrode, one negative electrode, and an anchor tether [80, 81]. The three helices are placed around the vagus nerve to deliver the electrical pulse of the pulse generator [82]. During surgery, the vagus nerve is electrically stimulated to test the impedance and functionality of the device, which can be accompanied by bradycardia and short-lasting systole [83, 84]. After implantation, VNS therapy can be initiated starting at a low dosage of stimulation with an output current of 0.25 mA [85, 86]. Dosage is increased slowly with steps of 0.25 mA to a maximum output current of 3.5 mA [87] because toleration to the stimulation is built up with the use of the VNS device [88, 89]. Implantation of the three helices around on the left vagus nerve containing a positive electrode, a negative electrode, and an anchor tether, which is shown in **Fig. 6**. The electrodes are connected to the lead, which is attached to the pulse generator [90, 91].

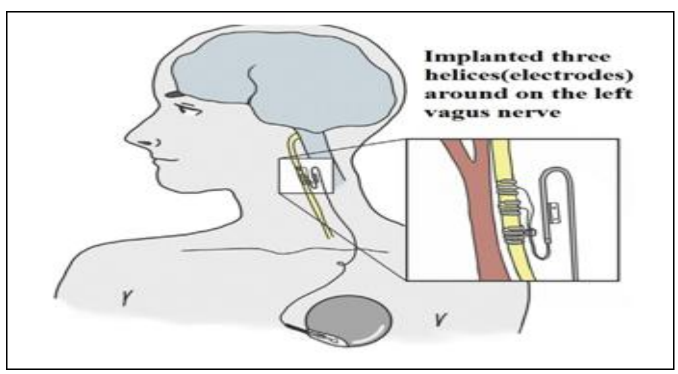

FIG. 6: IMPLANTATION OF THE THREE HELICES AROUND ON THE LEFT VAGUS NERVE CONTAINING A POSITIVE ELECTRODE, NEGATIVE ELECTRODE AND AN ANCHOR TETHER

4. Bioelectronic in Spinal Cord: Regaining motor function is of high priority to patients with spinal cord injury (SCI) [92]. A variety of electronic devices that interface with the brain or spinal cord, which have applications in neural prosthetics and neuro-rehabilitation are in development [93, 94]. Brain-machine interfaces that decode motor intentions from cortical signals are enabling patient-driven control of assistive devices such as computers and robotic prostheses [95], whereas electrical stimulation of the spinal cord and muscles can aid in retraining of motor circuits and improve residual capabilities in patients with SCI [96, 97]. Next-generation interfaces that combine recording and stimulating capabilities in so-called closed-loop devices [98, 99], like BMI (Brain-Machine Interfearance), which is shown in **Fig. 7**. Will further extend the potential for neuroelectronic augmentation of injured motor circuits [100, 101]. Emerging evidence suggests that integration of closed-loop interfaces into intentional motor behaviors has therapeutic benefits that outlast the use of these devices as prostheses [102, 103]. Brain-machine Interfearance: Brain-machine interfaces (BMIs) that record and decode signals from the brain enable volitional control of assistive devices [104, 105,] and modify patterns of cortical activity through the process of neurofeedback [106, 107]. The translation of invasive BMIs from animal studies to patients suggests that these technologies could control functional electrical stimulation for the restoration of movement to paralyzed limbs [108-110]. Functional limb movements involving the coordinated activity of multiple muscles [111-113] and the activation of spinal circuitry in combination with volitional intent could have therapeutic benefits [114,115].

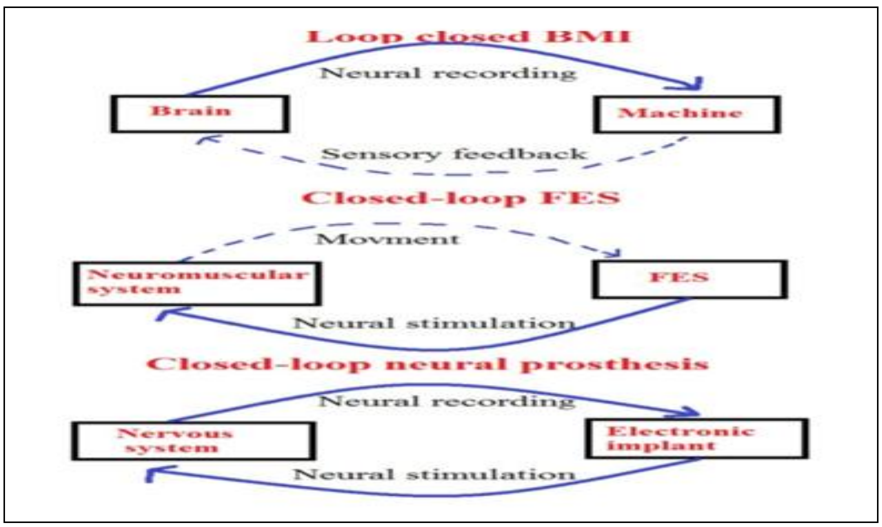

FIG. 7: CLOSED-LOOP DEVICES LIKE BMI

5. Bioelectronics in Blind Disease: For the treating retinal disease, bioelectronic medicine play critical role. Bioelectronic medicine it's a device that is implanted in the retina, which is shown in **Fig. 8**.

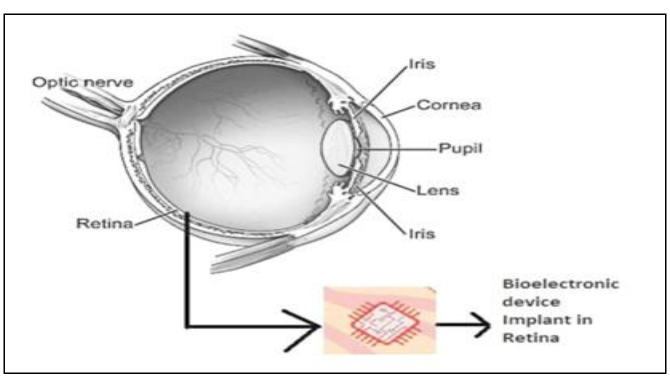

FIG. 8: BIOELECTRONIC IN BLIND DISEASE

It includes a retinal prosthesis for restoring vision to the blind, thereby significantly improving patient's quality of life. This implantation treated blind disease.

CONCLUSION: Recently, Bioelectronic is being used more widely to describe this multidisciplinary field. Progress is required in all of these sectors for innovation in cross-cutting areas, including measurement and characterization, fabrication, and power sources. That several technologies are now moving from preliminary clinical trials. Continued progress in the development of technologies for monitoring and manipulation of neural activity will, hopefully, lead to a new generation of devices to injured neural circuits. In this Review, we have discussed progress in the new field of bio-electronic medicine, and underlying neuro-physiological and other mechanisms make it possible to target specificcircuits to treat disease and improve affected organ functions. So, indeed bioelectronics is a career of the future, and it promises a lot to the general public, too, as electronics are very economical when they go into mass production. That prospect certainly promises a significant leap forward in both treatment safety and efficacy, by replacing electrons on the place of drugs.

ACKNOWLEDGEMENT: I profusely thankful to Prof. Dr. Sunita Chaudhary, Department of Pharmaceutics, Arihant School of Pharmacy and BRI, Gandhinagar, for their valuable suggestions and guidance.

CONFLICTS OF INTEREST: We declare that we have no conflict of interest.

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How to cite this article:
Patel DA and Chaudhary S: Bioelectronic medicines: innovation in disease treatment. Int J Pharm Sci & Res 2020; 11(9): 4229-37. doi: 10.13040/IJPSR.0975-8232.11(9).4229-37.