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Review

New insights into bioelectronic medicines: A new approach to tackle diabetic peripheral neuropathy pain in clinics

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ABSTRACT

Bioelectronic medicines are a newer way to treat and diagnose the diseases associated with biological systems. All vital organs of the body are innervated, commanding brain to regulate the homeostasis functions. Bioelectronic medicines rely on implications of electrical stimulations or signals associated with the nervous system for real-time treatment. Diabetic peripheral neuropathy (DPN) is a most prevalent micro-vascular complication associated with diabetes mellitus. Complex plexus of nerves were affected in this complication with impaired function. Bioelectronic medicines are future hope for effective treatment of DPN.

1. Introduction

Bioelectronic medicine is a revolution in the field of therapeutics. It takes advantage of the body's natural electrical impulses and signals to treat a disease. Bioelectronic medicines work by transmitting electrical impulses along nerve fibres as against to normal generic medicines which work on molecular mechanisms. If properly explored and implemented this idea can reduce the cost of medicine manufactured and administered worldwide as well as it will make breakthrough innovations in the field of healthcare. Another added advantage of bioelectronic medicines is that it requires minimum invasion for treatment and also will cause the least hindrance in the normal routine of the patient [1–4].

The central nervous system controls the function of each organ in the body. This control is achieved in the form of electric impulses running along the nerve fibres. Each organ is connected to the central nervous system by peripheral nerves. In case of a disease, these electrical impulses start behaving differently from their regular pattern. An electrical impulse in a healthy heart will be different from that having a chronic heart condition. Bioelectronic medicine restores the balance during disease condition by blocking or stimulating the nerve impulse thereby maintaining the normal pattern of their conductance. These tiny devices can be implanted on any individual nerve or a group of nerves. This approach aims at having effective treatment of the disease with fewer side effects which is found in the case of conventional medicines. Bioelectronic medicine exploits a natural pathway already occurring in the body and maintains the normal internal condition of the body. Hence it is a more natural approach for the treatment of any disease.

The bioelectronic medicine opens a plethora of possibilities to cure diseases because different action nerves can be targeted to cure a wide variety of diseases. For example, asthma could be treated while targeting the nerves that control bronchi constriction while scheming nerves in the pancreas could regulate insulin production to manage diabetes. Even nerves leading towards ovaries or tumours could be targeted to treat infertility and cancer. Bioelectronic medicines may also allow patients and their physicians to monitor health in real time.

Though the approach seems to be effective, yet there are various challenges in the way of it. Targeting a specific nerve can be tedious as they are mostly found in bundles. To discover the exact effect and signalling of any nerve could be rather challenging. Testing of the implanted device for its battery life and longevity is also going to be rather arduous.

A breakthrough research development occurred when vagus nerve was focused. It comprises of around lakhs of sensory and motor fibres leading to organs such as heart, lungs, pancreas, liver, kidney etc. Stimulating the vagus nerve has produced encouraging results in animal models in a range of diseases as it controls involuntary functions, such as breathing, digestion and heart rate

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[5–7]. Other studies are also in progress to prove the potential of bioelectronic medicine as the new saviour for patients in distress due to a wide number of diseases.

In July 2016, a clinical trial proved that when a part of the vagus nerve was electrically stimulated with an implantable bioelectronic device, there was a significant reduction in the symptoms in several patients of rheumatoid arthritis (RA), these patients also included those who failed to respond to any of the generic medicine for treatment (including methotrexate, tumour necrosis factor [TNF] agonists and biologics), with no serious side effects [8]. RA, a chronic inflammatory disease causes stiff, swollen and painful joints. Stimulating part of the vagus nerve that leads to the spleen for one to 4 min daily inhibited production of TNF, an inflammatory molecule targeted by many pharmaceutical drugs.

Joana F. Sacramento et al. [9] characterized the ability of a novel bioelectronic application, classified as kilohertz frequency alternating current (KHFAC) modulation, to suppress neural signals within the CSN of rodents. KHFAC modulation of the CSN improved metabolic control in rat models of type 2 diabetes.

Not only the bioelectronic medicine is proving their potential in the treatment of diseases but they are also being used for early detection of several diseases. Yen-WenChen et al. [10] reported the development of an efficient and sensitive method to directly sense microRNA (miRNA) in high ionic strength solutions with the use of electrical bilayer (EDL) gated AlGaN/GaN HEMT (high electron mobility transistor). This FET structure uses a complementary DNA probe functionalized gate electrode which is separated from the transistor channel. In this research, the focus was on the detection of miRNA samples, miR-126, miR-208a and miR-21 which are biomarkers of cardiovascular diseases (CVD). Selectivity of the sensor was demonstrated by evaluating sensor response at fully complementary and slightly mismatched sequences. The miniaturized sensor could be used in point of care or home care diagnostics for rapid miRNA detection to evaluate CVDs at an early stage.

According to Tzahi Cohen-Karni et al. [11] reported a unique transparent graphene-based electrical platform that enables concurrent electrical and optical investigation of ES-derived cardiomyocytes' intracellular processes and intercellular communication. This presented approach will surely contribute in the enhancement of our basic understanding of signal transduction in complex cellular assemblies, and create new avenues for bidirectional communication (sensing and stimulation) with electrically active tissues. ZhengpingLi et al. [12] reported photoelectrochemical (PEC) sensors based on carbon dots (CDs) which were developed for ultrasensitive detection of glutathione (GSH) without additional catalysts. CDs based hybrid nanocomposites are promising future candidates for the development of PEC biosensors with enhanced sensing performances.

2. Glimpses of diabetic peripheral neuropathy

Diabetic peripheral neuropathy is a diabetes mellitus induced disorder of the peripheral nervous system [13] and due to symmetrical degeneration of distal peripheral nerves, pain and loss of sensation take place. The symptoms will deteriorate with the progression, which may result in diabetic ulcers or even non-traumatic amputation. Statistics revealed that the incidence of Diabetic peripheral neuropathy was as high as 30%, 60%, and 90% at 5, 10, and 20 years after diagnosis of diabetes mellitus, and foot injury had occurred in 50% of Diabetic peripheral neuropathy patients when they were asymptomatic [14]. The incidence of neuropathy is now estimated to be about 8% in new cases of diabetes mellitus, and neuropathy will be a lifelong disease in more than 50% of diabetes mellitus patients, which is about 4 times figure (12.3%) in diabetes mellitus patients in 2001 [13–16]. Thus, Diabetic peripheral neuropathy has been an important economic burden of the medical system [17] and significantly influenced the quality of life of diabetes mellitus patients. To overcome all this, a new type therapeutic approach that allows a precise detection and modulation of electrical signalling patterns in the peripheral nervous system, known as bioelectronic medicine, is emerging [18–20]. Current therapeutic approaches currently available for metabolic diseases do not provide long-term control of the disease, combined with significant side effects, a bioelectronic medicine approach could bring significant improvement in the standard of care for diabetic peripheral neuropathy by targeting nodal metabolic pathways and avoiding systemic effects. Additionally, bioelectronic medicines might have high acceptance among patients given that they require only minimally invasive procedures while providing high adherence and negligible interference with daily activities [18–21].

Due to their numerous comorbidities, patients with diabetes mellitus may find it difficult to perform exercise training and therefore require other treatments. One method is electrotherapy [22–24], which has been shown to enhance microcirculation and endoneurial blood flow [24]. Electrotherapy is an effective therapy in regard to the impaired microcirculation in the peripheral nerves. Electrotherapy also increases muscle's oxidative capacity. Martin et al. [25] found electrical stimulation to exert an effect on the morphological and metabolic properties of paralysed muscles. Local release of neurotransmitters such as serotonin [26], increased production of mitochondrial adenosine triphosphate (ATP) [27], the release of endorphins [28], or anti-inflammatory effects [29] may also trigger the analgesic effect of electrotherapy. The input of pain is interrupted by the inhibition of C fibres (thus interrupting/gating the input of pain) [30]. Mima et al. [31] registered a reduction in the excitability of the human motor cortex by the use of high frequency transcutaneous electrical nerve stimulation (TENS); the study suggested that short-term TENS have an inhibitory effect on the sensory as well as the motor system. Various types of electrotherapy, such as transcutaneous electrical nerve stimulation (TENS) [32–36], pulsed-dose electrical stimulation applied by stocking electrodes [37,38], pulsed (electro-) magnetic fields [39–42], static magnetic field therapy [43], external muscle stimulation [44–46] and frequency-modulated electromagnetic neural stimulation (FREMS) [47], have been reported, but to our knowledge have not been reviewed thus far.

3. Role of bioelectronic medicines in diabetic peripheral neuropathy

3.1. Transcutaneous electrical nerve stimulation

Kumar & Marshall [32] evaluated the efficacy of TENS for the management of PN in patients with type 2 diabetes. In another single-blind, placebo-controlled, randomized study also known as 2-arm study; Kumar et al. [33] evaluated the efficacy of TENS in combination with amitriptyline for the management of PN in patients with type 2 diabetes. In was found that TENS in combination to amitriptyline was very effective than TENS alone in reducing pain in patients. In a further article, the same study group used the above-mentioned stimulation device to determine the long-term efficacy of TENS on neuropathic symptoms in diabetic patients [35]. For the retrospective analysis the authors used the device for 1.9 times per day for 34.7 min and the period of treatment was, on average, 1.7 years and found that 76% of the patients reported a $44 \pm 4\%$ subjective improvement in neuropathic pain.

A German working group performed a double-blind, randomized study comprising 19 patients with mild to moderate symptomatic diabetic neuropathy, and evaluated the treatment of TENS in comparison with placebo treatment [36].

3.2. Pulsed-dose electrical stimulation applied by stocking electrodes

In a pilot study, Armstrong et al. [37] evaluated pulsed-dose electrical stimulation as an analgesic modality in 10 patients with painful nocturnal diabetic neuropathy. A significant reduction in pain was noted after 4 weeks of treatment and at the follow-up evaluation 4 weeks after discontinuation of therapy. A previously published study done by Oyibo et al. [38] also used silver-plated nylon/Dacron stocking electrodes.

3.3. Pulsed (electro-) magnetic fields (PEMF/PMF) and static magnetic fields

Weintraub & Cole [33], enrolled 24 patients suffering from refractory neuropathic pain due to PN and later treated with PEMF. PN is an associated complication with diabetes (6 patients), pernicious anaemia (2 patients), chronic inflammatory demyelinating polyneuropathy (2 patients) or other conditions (14 patients). A short-term analgesic effect was achieved in more than 50% of the participants. Patients with more severe symptoms achieved greater benefits. The effect of placebo was not tested. Musaev et al. [40] evaluated the effects of PEMF and found a beneficial role in PN. At the termination of the study, pain intensity was reduced in both groups, and a significant alleviation of the major subjective symptoms of PN was noted. Wróbel et al. [41] studied the impact of low-frequency pulsed magnetic fields on the intensity of pain, quality of life, and sleep in patients with painful diabetic PN. Sixty-one patients were included in a randomized, placebo-controlled, double-blind trial. It was found that both study groups experienced a significant reduction in pain as measured on the VAS, but exposure to the magnetic field was in no way superior to sham therapy in a randomized, double-blind, placebo-controlled parallel study, Weintraub et al. [42] used PEMF in 225 patients with symptomatic diabetic peripheral neuropathy. A device delivering 1800 G by 6 individual magnetic sphere units (3 under each foot) was used for 2 h per day (in divided sessions of 10–30 min) over 3 months. The placebo group was treated with an inert, non-active demagnetized sham device. Another study conducted on 35 patients who underwent skin biopsies before and after PEMF treatment showed no significant differences between the PEMF and the sham group with regard to the intensity of NP on the NPS or VAS for pain and sleep scores. In a further randomized, double-blind, placebo-controlled trial, Weintraub et al. [43] registered analgesic benefits of static magnetic field therapy in 375 patients with diabetic neuropathy.

3.4. High-frequency external muscle stimulation, high-tone external muscle stimulation and external muscle stimulation (HF/HTEMS/EMS)

Reichstein et al. [44] compared the effects of high-frequency external muscle stimulation with those of TENS in 41 patients with diabetic PN. The electrodes for HF treatment were placed on the femoral muscles. Stimulation was performed with $\leq$350 mA, $\leq$ 70 V with an initial frequency of 4.096 Hz later increased to 32.768 Hz within 3 s time interval. In the TENS treatment group, the electrodes were placed on the lower extremities as described above [32]. It was found that there is a significant reduction in pain HF subjects compared to TENS.

Klassen et al. [45] aimed to determine whether HTEMS is effective in diabetic end-stage renal disease patients (25 patients) with symptomatic PN and whether uraemic PN (15 patients) is similarly modulated. Fourteen patients who had received haemodialysis were enrolled. For HTEMS the electrodes were placed on the femoral muscles, and in some cases on the calves as well. The stimulation parameters were similar to those used by Reichstein et al. [44]. In a prospective, uncontrolled trial Humpert et al. [46] evaluated the effect of external muscle stimulation (EMS) in patients with type 2 diabetes and diabetic neuropathy.

3.5. Frequency-modulated electromagnetic neural stimulation (FREMS)

In a randomized, double-blind, crossover study, Bosi et al. [47] examined the effects of FREMS in 31 patients with painful diabetic neuropathy. Placebo treatment consisted of no electrical current transmission. FREMS showed a significant reduction in pain (VAS), a significant increase in sensory tactile perception, a decrease in foot vibration perception threshold, and an increase in motor nerve conduction velocity. It also stated that treatment was safe and effective for peripheral nerve function.

4. Conclusion

In this paper, we discussed some of the newer applications of bioelectronic medicines in the field of diabetic peripheral neuropathy. This review is not meant to be exhaustive, but rather to give the reader an excellent technical understanding about the various therapies currently available for the effective treatment of diabetic peripheral neuropathy. We have focused several electrical stimulation approaches that are effective in peripheral nerve regeneration. These newer interventions in bioelectronic medicines can be a newer hope for improving life care of diabetic peripheral neuropathy subjects and can be future hope for curing DPN.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.021.

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