Journal of Pharmaceutical Research International

32(33): 23-31, 2020; Article no.JPRI.63370
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Bioelectronic Implants and Their Role in Modern Medicine

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Authors' contributions

This work was carried out in collaboration among all authors. Author EVN designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AOL and HA managed the analyses of the study. Authors TT and MA managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2020/v32i3330945
Editor(s):
(1) Dr. Mohamed Fathy, Assiut University, Egypt.
Reviewers:
(1) José Ednésio da Cruz Freire, Federal University of Ceará, Brazil.
(2) Kristina Ramanauskiene, Lithuanian University of Health Sciences, Lithuania.
Complete Peer review History: http://www.sdiarticle4.com/review-history/63370

Review Article

Received 25 September 2020
Accepted 30 November 2020
Published 08 December 2020

ABSTRACT

Humanity turned to medicines millions of years ago, when medicinal plants were used for healing. In the century before last, a significant contribution to medicine was made by various fields of science; in particular, here one can name a device that has long been used to deliver medicine to the body – a syringe.

Today, the use of injections of drugs of biological origin is a common practice for the treatment of chronic diseases, but the injection procedure itself is often associated with painful perceptions, and the field of injection is limited. Modern advanced therapies are genetic, electronic and cellular therapies that can meet the needs of caregivers, as well as the patients themselves.

It is well known that digital processes in healthcare are currently undergoing intensive development, and in this context, innovative bioelectronic devices are being used to implement new strategies for personalized injection therapy. This paper examines aspects of the development of innovative methods of drug delivery to the patient's body, such as optogenetic therapy, optogenetic

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methods, and genetic therapy. For these purposes, bioelectronic implants are used today, in which electronics and optogenetics interact with the help of light, transmitting a certain induction signal to each other. By controlling the synthetic optogenetic pathway in the cell, drugs can be delivered to a particular organ within a clearly limited space or time.
Present technology is revolutionary in medicine, as it can replace a traditional syringe, increasing the accuracy of dosage and time of drug administration, while reducing the involvement of the human factor to a minimum. The technology under consideration also acts as minimally invasive, which minimizes the patient's discomfort when taking medications.

Keywords: Bioelectronic implants; syringe; genetics; optogenetic pathway; synergy.

1. INTRODUCTION

Modern medicine is a synergetic synthesis of the development of devices for injecting drugs into the body and an ever-growing body of information in the field of applied and theoretical pharmaceutical research. So, F. Rind in 1844 wrote a work on the infusion of fluids into the human body using a syringe. This study allowed us to develop a device for the introduction of subcutaneous and intravenous injections, and also made it possible to study the systemic mechanism of action of painkillers that are injected directly into the circulatory system.

This discovery also had negative consequences: the exact route of administration of opiates (intravenous injections) was adopted by drug addicts, who began to use for this purpose repeated injection of narcotic drugs into the body [1-4].

The first targeted preventive use of syringes was not limited to chronic pain. Due to the limited effect of early insulin medications, diabetic patients had to be injected several times a day. Later, through the intravenous administration of penicillin during world war II, vital injections were popularized [4-5].

Initially, in the 18th century, a syringe was a glass product that was made by hand. Later, glass Spitz was manufactured by the factory, but their use was reusable, which without proper organization of sterilization could cause the spread of a number of infections [6-10].

In 1970, plastic disposable insulin syringes appeared on the market, after which the production of disposable syringes for various medical purposes became widespread all over the world [11-15].

In the modern world, the number of chronic diseases is constantly growing, most of which are associated with the wrong lifestyle of people. These are diseases such as obesity, heart disease, stroke, cancer, type 2 diabetes, and arthritis). Accordingly, for each of these diseases, the volume of medications taken by patients is constantly growing [16-20]. Doctors fear that after 2022, chronic diseases will cause almost three-quarters of all deaths on Earth, which is why it is necessary to increase control over the management of a particular patient and, first of all, by increasing the effectiveness of injecting therapy with certain medicines [21-23].

One of the ways suggested by the authors was the use of an alternative to injecting therapy, such as gene therapy. However, research in this area has not yet come to a logical end [24-26].

In addition, the risk of gene intervention in the case of cell transplantation is very high, and all this requires that patients who have undergone gene therapy are examined for life.

Modern medical devices are closely linked to innovations in electronics and photonics. In particular, constantly developing medical technologies, which were used to create a pacemaker, as well as the ability to perform electroencephalograms (EEG), made it possible to develop an innovative approach, the purpose of which was to create a bionic heart, as well as the formation of a brain-computer interface [27-30].

Also, to date, many works are devoted to the study of implantation issues as such, which are used in various fields of modern medicine, including in regenerative medicine [31,32].

One of the areas in this field that is being used quite successfully today is brain mapping. Brain mapping is a magnetoencephalographic (MEG) system designed for high-precision 3-dimensional mapping of brain structures in real

time (non-invasively). MEG technology is used for both clinical and research purposes. Pre-surgical mapping for neurosurgery, when combined with MEG and MAGNETIC RESONANCE IMAGING (MRI), improves the accuracy of surgical navigation and radiotherapy planning. The use of 306 magnetoencephalographic (MEG) and 64 electroencephalographic (EEG) channels provides high-precision localization of functional areas of the cerebral cortex [33-37].

Research and brain mapping have opened up new horizons in genetic engineering. To decipher neural maps, synthetic biology researchers are developing a set of optogenetic tools. Genetic reprogramming introduces a photoactivated molecular activator 4,5 into the genome of neuron to shed light on neural network structures. This technology has not yet been widely applied in practice.

In 2016, the Food and Drug Administration (FDA) approved only 15% of innovative molecular units that are personalized medicines. And work in this direction continues to this day [38,39].

Genetically engineered therapeutic proteins (antibodies, interleukins, peptides) are a unique class of drugs called biologics. On the one hand, biologics are difficult to produce, since this requires complex biotechnological installations that have passed factory tests, on the other hand, they have a higher target specificity, and their use reduces side effects, all this makes it possible to talk about the effectiveness of these drugs already at the preclinical stages of research [22].

A promising task of medical science is to create a device that could act as a full-fledged replacement for a syringe. This is a so-called implantable device that can deliver medicine to any organ of the human body. Shipping is based on optogenetic: this system links the optically controlled bio-production of therapeutic protein and its perfusion in the circulatory system. The technology gets its name from optogenetics and gene therapy [40].

A multidisciplinary optogenesis device that combines achievements in cell encapsulation, optogenetics, and electronic engineering could find its place in a globalized, futuristic bio-cybernetic e-health [33,41,42].

This technology allows one to control the human body in a closed cycle, monitoring the chronic condition together with a chain of biosensors that are connected to remote telemedicine. Let us consider the main stages of development of bioelectronic implants in modern medicine.

The purpose of the study is to consider the role of bioelectronic implants in modern medicine.

2. A BRIEF REVIEW OF THE METHODS USED FOR THE PROGRESS IN MODERN MEDICINE

The first stage in the development of a cell-based drug delivery device for tomorrow is the continuous development of cell transplantation therapy, which was initially used for the treatment of diabetes, and then began to be used for the treatment of other types of diseases.

In 1921, it was determined that the hormone insulin can be successfully used for the treatment of diabetes, but it was also found that therapy with the use of insulin to get the effect must be long-term. This medicine in tablet form is not used by patients, therefore, it must be administered by injection. Despite significant research efforts by a major medical device manufacturer such as Medtronic to develop an advanced personalized closed-loop strategy, alternative injection therapy options are still limited today [24].

Thus, one of the methods of treatment was a complete pancreatic transplant, but in this case, permanent immunosuppressive treatment was required. However, this type of therapy did not provide a long-term solution due to the increased risk of incoming infections and potential causes of cancer. For this reason, instead of the entire pancreas, the therapy was aimed at isolating the islets of Langerhans from the pancreas.

One of the solutions to islet transplantation was to use immune privileged sites, i.e. protected from immune destruction. It has been demonstrated that these sites allow the Islands to take root in order to stay in place longer before immune rejection from the patient occurs [29].

In 1933, Bichelier was the first to propose the treatment of diabetes with encapsulated insulinoma. Later, when studying immune rejection, researchers evaluated the ability to encapsulate islands in the membrane with different pore sizes. The idea was to prevent immune rejection by circulating cells. As a result of their research, a chamber with a small pore

diameter (<0.45 microns) was created, which is able to provide immune protection for islets. This strategy of retaining a semipermeable membrane offers a double advantage; on the one hand, immune cells cannot penetrate the pores of the membrane; on the other hand, oxygen and nutrients can pass through and supply the cells [33].

The concept of optogenetics emerged after the development of the fields of cell therapy, electronics, and synthetic biology. Cell therapy, based on advances in encapsulated cells for diabetes therapy, predestined the appearance of a cell implant. Electronic medical devices, which date back to the development of pacemakers, have made it possible to produce medicines wirelessly (microchips). Finally, synthetic biology and optogenetics allow us to control the ability of cells to produce protein simply by using light. Optogenetics, as a multidisciplinary approach, consists of an implant based on bioelectronic cells with wireless power to create an optoelectronic circuit. It triggers the bio-production and release of therapeutic protein by engineered cells [27].

Various authors describe positive examples demonstrating successful islet transplantation to various animal models and patients. Modern methods provide selective permeability by using intravascular or extravascular macro devices surrounding the islets, as well as micro devices containing fewer encapsulated islets, coatings made of a material that is selective in permeability, and finally nanoincapsulation to protect each islet.

Micro devices place a small number of islets in the hydrogel. Various semi-permeable encapsulation materials are used to isolate the implanted cells from the host, such as alginate, which is most popular for its excellent biocompatibility and ease of use, as well as agarose, cellulose, chitosan, and other materials.

In contrast to the encapsulation of alginate and hydrogels, which cannot be explanted, membrane restriction provides maximum safety for the patient, since genetically modified cells do not circulate in the vascular system, and the device can be removed at any time [11].

Macro devices first appeared on the market in the late 1990s thanks to Baxter Healthcare. The company also holds a patent for the development of the TheraCyte implant. The structure of the device is represented by Teflon membranes and polyester mesh, which provide neovascularization after implantation [41].

Research on rodents has been successful, but has not been applied in clinical practice among humans. At the same time, a small biotech company, Islet Sheet Device, used an alginate sheet to encapsulate the islets. Among the main difficulties in beta-cell transplantation should be called ischemia. Since insufficient oxygenation due to lack of vascularization remains one of the main reasons for implant failure. Beta-O2 devices focus their efforts on developing methods to improve device oxygenation by injecting or producing oxygen [35].

3. A BRIEF REVIEW OF THERAPEUTIC PROGRESS IN MODERN MEDICINE

After the success of cell therapy based on islet transplantation, the field of cell implants has become of interest to therapists in the treatment of several types of diseases. In 2002, an experimental introduction of encapsulated PC-12 (cell line derived from pheochromocytoma of the rat adrenal medulla) cells into a hollow fiber membrane was performed, allowing the release of a neurotransmitter in order to quantify the level of dopamine in culture. When measuring the permeability of the membrane, they also demonstrate its ability to release neurotransmitter. They further improved the design of their technology by implanting a reusable cell encapsulation device and testing it on rat brains as a treatment for Parkinson's disease.

In addition, it is necessary to consider using the encapsulation method in order to relieve chronic pain. Cattle cells were isolated and then implanted in a sheep for six weeks. The cells were able to secrete norepinephrine and meth-enkephalin [7].

The production of biologics laid the foundation for the empirical technology of selecting lines of super-producers. Recent advances in genetic engineering contribute to the further improvement of the technology with the help of special genome editing tools. Synthetic biology applied to encapsulated cell technology has evolved into an innovative therapeutic platform for the production of biologics directly at the point of delivery. Thus, the host does not face the risk associated with direct genetic modifications or perfusion of genetically modified cells in the

body. Genetically modified cells are reliably isolated from the host [2].

As a means to treat Alzheimer's disease, epithelial cells were developed, their goal was to intensify the growth of nerve endings. The result was evaluated for 12 months in laboratory conditions on mini-pigs.

The technology has been further improved by developing a special cell framework that supports the growth of a similar tissue structure in the implant chamber.

The cell-based device has been successfully tested on patients with Alzheimer's disease. Four patients were implanted with a device containing cells capable of releasing nerve growth factor for six months. The safety and effectiveness of the technology were evaluated after the devices were extracted from one of the patients for analysis.

Experts have also investigated and proven the effectiveness of monoclonal antibodies that fight against amyloid, these bodies have also been used as therapy against Alzheimer's disease. The macroencapsulation device developed as part of the experiment described above successfully secreted antiamyloid antibodies in a rodent model on animals [16].

This technology can be used for the treatment of various diseases, such as multiple sclerosis, blood-stroke, epilepsy, Parkinson's disease, Huntington's disease, etc.

Since cells can be designed to produce and deliver selected therapeutic drugs, cell encapsulation is an excellent method for obtaining and delivering drugs directly to the patient. Compared to a" traditional syringe", there is no need to produce medications or galenic formulations before implantation. Since cells can grow continuously, unlimited availability of drugs is assumed [25].

Also, in the framework of this work, it is interesting to consider a number of electronic medical devices. Electronic medical devices, such as pacemakers, have been around for 50 years. Before implantation, pacemakers were large portable devices capable of transmitting electrical impulses. In 1957, the first battery-powered wearable pacemaker was developed.

Innovations in medical devices are constantly evolving, researchers from Harvard University have developed a soft robot that surrounds the heart and is able to compress the organ, stabilizing its beating. The Carmat heart bioprosthesis is currently undergoing phase III clinical trials [24].

Most implanted electronic devices generate electricity as a therapeutic effect (pacemaker, deep brain stimulators, gastric stimulators). Using precision electronics to program drug delivery would provide additional control over corrective actions and better patient acceptance.

Indeed, repeated injections of therapeutic agents are painful for patients and lead to poor adherence to treatment. In recent years, control of the microchip wireless drug delivery implant has been achieved in medicine. The microchip consists of multiple drug doses divided into reservoirs that can be opened at will by electrothermal ablation of the surrounding membrane [10].

Eight women were implanted with the device for four months, and their use demonstrated effective release of human parathyroid hormone in areas such as the treatment of osteoporosis.

Another drug delivery device combines a closed-loop system in which an insulin pump can release insulin from a catheter programmed with a wearable glucose biosensor. In the future, this interface may be integrated into a network of connected biosensors that will eventually be connected to the Internet. This corresponds to a growing network of connected objects that can exchange data and coordinate controlled parameters.

Innovations in electronics continue to evolve and overcome current challenges that hinder the transition to effective medical devices. One of the main problems of electronic medical devices is the constant need for charging. In the case of miniature devices, the use of batteries creates difficulties due to their short service life and the large space required to implement this component [6].

Scientists in this field are trying to implement an old engineering principle discovered by Nikola Tesla - the transmission of energy through the air. The solution is to wirelessly transmit the power generator to an external source. The emitter coil synchronizes the power generation in the antenna that collects the implant's energy. Wireless power transmission relies on an

electromagnetic field to transmit power to the miniature implant. The technology provides not only electrical power to the device, but also a possible communication route between the emitter and receiver.

The field of electrical engineering offers new opportunities and tools for developing implantable miniature devices that can work as transceivers. For example, modern brain computer interfaces (BCI) are connected to a joint prosthesis. Paralyzed patients can take control of a prosthetic arm by focusing their attention on a task for the brain. The electrical activity of the brain is revealed using complex algorithms and is used for programming the computer interface [18].

As part of the research, it will also be interesting to analyze developments in the field of synthetic biology and optogenetics.

The engineering approach of synthetic biology often uses the vocabulary of electrical engineering to describe the behavior of the gene network and bio-calculators. Constructor cells can be a program for performing simple switching to more complex tasks, such as calculating a logical element.

Modern gene networks use modeling to support the Assembly of the following elements, such as:

– Analog to Digital Converter;
– Oscillator;
– Two-pole switch with double stroke (Double Pole Double Throw - DPDT);
- Necessary modules for building the model [14].

Genetic engineering offers the possibility of creating reliable regulatory pathways for Bioprocess processes, but also for programming the future of cells.

For therapeutic use, cells can be programmed to detect the level of a disease marker and receive an appropriate response by secreting a therapeutic protein. A proof of concept of this theranostics gene network was demonstrated during the organization of the treatment of the following diseases:

– Gouty arthritis;
– Thyroid disease;
– Diabetes;
– Psoriasis [19].

Light sensor proteins can serve as a genetically encoded optically controlled switch. Light exposure activates a synthetic pathway to trigger cellular potential, as well as to control gene expression via the second messenger signaling pathway.

Light can be used to trigger the expression of a single protein, but it can also be used to control an organ or synchronize cellular behavior.

Cell implants that respond to blue light were developed based on hollow fibers containing blue light-sensitive cells [14].

The cytotoxic properties of blue light and difficulties in accurately dosing the gene response using transdermal light illumination led to the study of a different gene network system controlled by synthetic light. A near-infrared (NIR) bioluminescence source implanted in the brain shows promising results for new treatments aimed at preventing neurodegeneration. Using NIR as a traceless inducer of the gene network is also an attractive strategy for controlling the nucleotide cyclase domains associated with bacteriophytochrome. Using secondary messenger pathways, prokaryotic phytochrom can control the pathways of eukaryotic innate immune response or interact with specific chimeric transactivator proteins.

The concept of "optogenetic therapy" arises as an innovative cell implant for managing the introduction of biologics. It consists of a synergy of Mature technologies in the field of microencapsulation, electronics, and optogenetics. In contrast to the previous approaches, the device has an integrated electronic module. This is the first of its kind, as it binds genetically modified cells protected from the immune system thanks to semi-permeable membranes and an optoelectronic interface to control the cellular behavior enclosed in the implant. All implanted therapeutic devices so far have consisted of either only electronic or only encapsulated cells, but not a combination of these two regions. The electronic module that controls the light source is used as a trigger for light-sensitive design cells [4].

The energy-harvesting antenna feeds the cell-based implant with wireless power. Its remote control gives the practitioner complete control over the infusion therapy. The device can play a fundamental role in many therapeutic applications. Integration of the implanted module

to optogenetic in a network of electronic biosensors will form the basis for new digital therapeutic processes. Miniature wearable biosensors that measure patient parameters are already available in clothing and will contribute to the development of future e-health platforms [33].

In the field of wearable biosensors, algorithms are being developed that will integrate patient commands recorded using EEG devices. Now with a wearable BCI, you can control the lightning switch or control a wheelchair just by thinking.

As a proof of concept for an optogeneration device, the BCI interface was used to program the secretion of a reporter protein marker in the bloodstream of a rodent model on animals placed on a wireless transmitter. A human user wearing an EEG headset performed a mental task to wirelessly control the lighting time of an implanted cellular device in mice. The experiment confirmed that it is possible to "control the mind" of an implanted micro-processor with wireless control, using the signal received from the biosensor [42-47].

The biosensor can directly measure a disease marker, such as glucose levels, in patients with type 2 diabetes. The researchers took advantage of optogeneration technology to isolate glucagon-like peptide 1 (GLP-1) in a rodent model of diabetes.

In the experimental setup, glucose monitoring data is integrated via a mobile phone platform into a closed-loop system similar to the Medtronic insulin pump, except that the wearable biosensor triggers an implanted led with wireless power [14].

The transfer of optogenesis technology from the laboratory to the hospital requires the development of small-scale production of universal design cells in accordance with Good Manufacturing Practices (GMP) and outpatient device implantation procedures. Each cell type will be designed according to the target disease and the patient's needs. An external wearable device that controls the implant will help the patient and practitioner fine-tune infusion therapy [11].

4. CONCLUSIONS

In our opinion, continuous improvement of cell therapy has made it possible to learn about the possible pathway of cell engraftment using macro capsulation devices. In the case of diabetes, difficulties in implanting islets are associated with recreating a specific niche for cells. Even after implantation, the disease is still present and actively affects beta cells. Recent advances in genetic engineering may help develop alternative strategies for treating diabetes.

We strongly believe that achievements in the field of electronic medical devices and the development of optogenetic instruments open prospects for the creation of the implant to orthogenesis. Inside the bioelectronic implant, electronic components connected wirelessly turn on an led to activate engineered cells that can respond to light and trigger the release of therapeutic agents.

Confirmation of the concepts of optogenetic therapy has demonstrated that the following can be used to control an implant based on wireless cells:

- Brain-computer interface for controlled drug delivery;
- Connected glucose biosensor for therapeutic diabetes control.

We consider that in the future, cell engineering is focused on research to determine the best engraftment and neovascularization of the parameters that are necessary for the success of implanted bioelectronic devices.

The ultimate goal is to create a closed regulatory system that recognizes the disease marker and, as a result, reacts by releasing the therapeutic drug in a precise and controlled amount. Optogenetic implant placing aims to act as future bio-cybernetic syringes that independently regulate the human body.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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