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BIOELECTRONIC MEDICINE FOR DIABETES MANAGEMENTS

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Abstract:

The novel treatments for serious health disorders are basically the modulation of the nervous system by delivering electrical or pharmaceutical agents. The advancement in research has development a new therapeutic approach called bioelectronic medicines. The nervous system uses electrical signals to transfer information throughout the body. Almost each cell and organ of the body is directly or indirectly controlled by these neural signals. In bioelectronic medicine peripheral nerve interface are a central technology because these medical devices can record modulate the activity of nerves that innervate visceral organs. Glucose homeostasis is regulate by the nervous system. This has new exploration investigating the chance of bioelectronic medicine for improving glucose control in individuals with diabetes, including regulation of gastric emptying, insulin sensitivity and secretion of pancreatic hormones. Besides, the development of novel closed-loop strategies aims to provide effective, specific and safe interfacing with nervous system and thereby targeting the organs of interest. In this article, we study the future aspect that bioelectronic medicine treatment for diabetes.

History:

In 18th century Luigi Galvani was the scientist who study the first bioelectronic, he applied voltage to pair of detached frog legs. The movement of leg through the sparking genesis of bioelectronic.[1] The Electronic technology has been enter toward biology and medicines since the pacemaker was invented. The bioelectronics research has been conducted by Dr. Kelvin Tracey of the Feinstein Institute for Medical Research in North well Health (New York) was discovered the inflammatory reflex, a neural circuit between the brain and the vagus nerve regulating the immune system.[2]

Definition:

Bioelectronic medicine are capable to exchange and modulate neural signaling pattern, succeeding therapeutic effects that are targeted at single function of specific organs. The main role of bioelectronic medicine is electron transfer.

Introduction:

The nervous system has major role to maintain a homeostasis for stability and self-adjustments of physiological state. For maintaining the homeostasis they use close-loop mechanisms called as neural reflex. It is a biological process of every living organism. It provides monitoring, response and regulation of all systems in human body as well as in other organisms. These containing sensing, integration and effector circuitries that modulate the organ task.[3]

Modulation of the nervous system through delivery of electrical or pharmaceutical agents has allowed the development of effective treatments to several severe clinical condition. The bioelectronic medicine has the ambitions to provide real-time and patient specific therapies by modulating the activity of specific peripheral nerves to improve or restore impaired biological function of specific organs.[4]

The therapeutic impact of bioelectronic medicine can be enhanced by replicating the body's closed-loop mechanism: metabolic and neurophysiological biomarkers can be recorded and analyzed in real time to accordingly adjust the characteristic of the electrical stimulation convey to the peripheral nerve or directly to the organs in order to modulate their function. The advancement in bioelectronic medicine are supported by development of new implantable technology which is safe effective and invasive interface with the nervous system.[5,6]

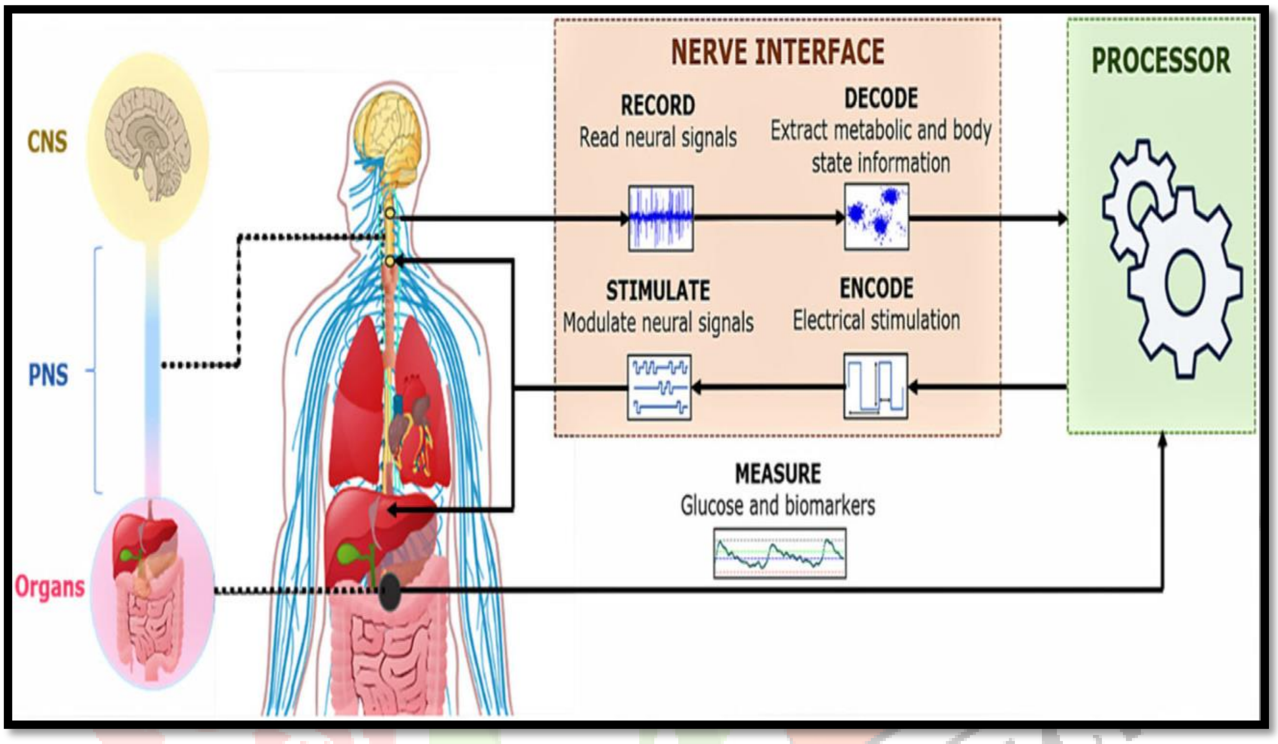

Fig.1 Bioelectronic medicine neuromodulation systems for diabetes management.

Diabetes is a chronic metabolic disease which is caused by the impairment of insulin hormone that result elevated in blood glucose. Currently there are 422 million people are affected by diabetes disorder through out the worldwide and it is 7th leading cause of death in 2030.[7] Therapies for type I diabetes are involve insulin administration. Whereas for type II, insulin administration in early stage but it is critical at later stages of the disease. The cost of insulin are unstoppable and it gradually increases, where as it is poised to reach up to $39.13 billion by 2020 based on the 2016 market research report published by Market sandMarkets.[8] The American Diabetes Association reported in March 2018 that the total costs of treating people diagnosed with diabetes has risen to $327 billion in 2017 from $245 billion in 2012.[9] These result reflect the impact of diabetes on society and encourage the development of new treatments to improve the control of glucose. The bio-electronic medicine are the treatment for diabetes it previously criticized by some members of scientific community underlying through biological process. However, current work demonstrated the vital role of the vagus nerve in the pathophysiology of diabetes, its comorbidities and supports the potential benefits of modulating the peripheral nerve signals to progress the metabolic dysregulation.[10,11]

Research related to glucose controlled:

Research related on bioelectronic medicine for diabetes control has emerged recently by two area of interest:

1) Recording from the peripheral nerve to extract metabolic information.
2) Improvement of glycemic fluctuation by modulating their electrical activity.[12,13]

The aim to use the vagus nerve as a glucometer to identify hypoglycemic events from neural reading. The neural activity presents a negatively correlated response to glycaemia. The complexity of recorded data requires advance strategies to identify and decode neural signals related to glycemic levels. Development of algorithm that recreates blood glucose levels with high accuracy using regression models with regularization to avoid over-fitting.[13]

Bioelectronics medicine study on diabetic rats. The acute electrical stimulation of the parenchyma tissue of the liver for 90min resulted in a decline together fasting and postprandial glucose levels in the healthy state of type I and type II diabetic rats. It shows continuous stimulation for 8 h during 4 consecutive days it shows decrease glucose level in 3 groups, delayed gastric empty and increased plasma glucagon-like peptide-1 (GLP-1) level. Adverse effect were not shown in result and it is feasible safe approach for glycemic control.[14]

Majority of research related to glucose control, neuromodulation that occurs due to metabolic disorders, food intake managing obesity and control of appetite. The gastric pacemakers are the technique which is stimulate the gastric myoelectrical activity is known as gastric pacing. Example the delivery of high frequency and short pulse width vagal stimulation in human clinical studies with the Transcend gastric pacemaker decrease the efferent vagal activity to the stomach, which caused increased gastric distension and slow gastric emptying. These change led to earlier satiety and even a reduction of food intake. A report shows that there are 20 to 40% of weight loss depending upon patient. These shows that the gastric pacing support further research on direct modulation of vagal activity known as vagal pacing. Human study in patients using vagus nerve stimulation to treat epilepsy and it is reported variety of responses, such as slightly more than 50% of patients losing between 5 to 10% of body weight. The new strategies automatically modulate vagal activity in response to stomach distension and hormones. The study in a rat successfully reported that 38% of body weight decline by delivering biphasic electric pulses based on the peristalsis measured on the stomach.[15]

Selective electrical activation or blockade of specific vagal fibers to specific organs has been shown to be a way to impact different metabolic process resulting in different glycemic outcome. Vagal blocking of afferent/efferent fiber has been experimentally achieved by direct transection of the vagus nerve, however this methodology cannot be translated into clinical research in humans.[16]

Future Prospective:

In bioeletronic medicine studies, by regulating the nervous system, there are many opportunities to target the processes and organs involved in the glucose-response reflex. The latest research has given insight into neural control of the liver and its implication of the balance of hepatic glucose production and uptake. As a result, modulating the neural signals to the liver would reduce the risk of hypoglycaemic events, especially for type 1 diabetes, by enhancing endogenous glucose production, which would rapidly increase glucose levels.[17]

The nervous system control the secretion of hormones from pancreas.[18] These neural pathways control to regulate the secretion of insulin and glucagon in patients with type 2 diabetes and early stages of type 1 diabetes, where there are still a considerable number of β-cell intact. This can be desirable in situation where glucose control in diabetic subjects is challenging, such as during exercise, which results in a decrease in glucose levels. Prompt inhibition of insulin secretion and promotion of counterregulatory hormone secretion (such as glucagon) before starting exercise may also be used to improve control of glucose fluctuation and reduce the risk of hypoglycaemia.

The neuromodulation of pancreatic secretion can be further applied in patients with stem cell-derived β-cell transplants. This strategy has been found to in preclinical trials to improve glycaemic control, but many challenges have not been resolved, including restoration of vascularization and neural innervation. Successful advances are being made in the former, but full restoration of the functionality of transplanted islets is still far from optimal. The development of biocircuit-augumented islet transplants containing mature vascularized and neural innervated β-cell, where neurons will grow inside hydrogel-based micro tissue engineered neural network scaffolds. We proposed bringing this idea one step further and using closed-loop neuromodulation of neural bio-circuits to restore the physiologic response to neural signaling that is present in healthy individual.[17,19]

The control of insulin sensitivity through neuromodulation, although usually associated with type 2 diabetes, can be further extended for use in people with type 1 diabetes. These subjects need external insulin injection after a meals to reduce glucose levels. Regulation of neural pathways can increase the role of this exogenous insulin in lowering blood glucose (i.e insulin sensitivity). As mention earlier, vagus nerve recording can also be used as a monitoring tool of the glycaemic status to detect disease and control its progression.[20]

As a final point, it is essential to consider the integration of this novel strategy for glucose control with the systems that are currently implemented for diabetes management. In particular, closed-loop systems for insulin delivery, such as artificial pancreas, are regarded as cutting-edge technology in glucose management for diabetes. An artificial pancrease comprises a sensor for continuous glucose monitoring, an insulin pump and an algorithm that replicates the endocrine function of healthy pancreas and calculates the optimal dose to be delivered based on the real-time glucose readings from sensor. One of the most employed artificial pancreas system is the Medtronic 670G, which is approved by US Food and Drug for use in people with types 1 diabetes over 12 years of age and is also CE Mark approved for use in people over 7 years of age within Europe.[21] Despite the developed glycaemic control recently reported in clinical trials, the system is still not entirely autonomous and requires user input, especially during meal intake. Combining the opportunities provided by bioelectronic medicine for diabetes will undoubtedly improve computation of the insulin doses, increased autonomy and personalized glucose control.

Challenges:

The bioelectronic medicine improve the current and future opportunities for treatment of diabetes, which is further benefit from the incorporation of a "closed-loop" control of both the immune and metabolic reflexes. That said, some important challenges and advance must be dressed in order to translate these strategies into real closed-loop therapeutic approaches.

Selective activation of the specific neural fibers that target the biological processes of interest is a major requirement to minimize the risk of undesired activation of other tissue, organs and processes. This entails the development of new stimulation approaches and devices to allow access and modulation of the activity of individual fibers. This difficulties is related with the issue of transferability, between species, yet in addition among nerves and tissue in the similar species, emerges from anatomical and conduction contrast among nerve fibers in the peripheral nervous system, which can influence their sensitivity and response to electrical stimulation.[22] For instance, the pancreatic branch contrast from the gastric-anticipating neurons in that they have i)longer duration of action potentials, ii)longer after-hyperpolarization decay time, iii)smaller soma area and iv)large diameter.[23] More research is expected to defeat this constraint, as only hypothetical extrapolation of the results is possible due to a lack of studies providing a comprehensive view of the similarities/divergence of parameter between nerve fibers and species.

The electrodes-nerve interface and design of new electrodes materials and fabrication strategies that confirm protection during stimulation, reliability during chronic recording, full biostability and biocompatibility with other tissue, whereas it must long term preservation of their functionality.[22]

Bioeletronic medicine must be have capability to improved neural decoding algorithms, coupled with advances in data analysis techniques, are allowing us to extract real-time information about the state of the nerve and related organs.[24]

Current artificial pancreas systems also have several challenges that need to be addressed if they are to be used in conjunction with bioelectronics medicine. Among them, the delays in interstitial glucose sensing and hormonal subcutaneous absorption, failures in the insulin pump and glycaemic control during meals and exercise are the most critical. Despite these difficulties, the use of the artificial pancreas is associated with high levels of satisfaction and quality of life and reduced fear of hypoglycaemic events among the diabetic patients. Moreover, there are ongoing strategies for educating the users to understand and operate these close-loop system. These perception propose that novel innovation technology integrating closed-loop neuromodulation and metabolic framework will be proficiently actualized and effectively received by the diabetes community. To achieve the desired state that restores or maintains homeostatis.[25]

Conclusion:

Bioelectronic medicine is a new pathway to treat diabetes patient. In future this will become reality and easily available for diagnostic and treatment of diabetes patient. Bioeletronic medicine is new therapy, however medicine and technology should work synchrony. Advances in minimally invasive technology to reliably interface with nervous system are needed to take us one step closer to using bioelectronic therapies for optimal metabolic control in daily life. According, it is crucial to fully understand the biological processes that underlie the glucose-response reflex to enables the creation of more efficient and safe systems.

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