

Neuromodulation – the future of diabetes treatments

The treatments for type 2 diabetes are limited in breadth and effectiveness. Medications have side effects, and many patients forget to take their medications regularly. An alternative treatment option that does not require daily compliance could provide better outcomes and is more likely to be used by patients. Dr Jonathan Waataja of ReShape Lifesciences in California, USA and colleagues have focused their efforts on devising new ways to tackle the issue – by stimulating key nerves which are involved in blood sugar control. Their groundbreaking work on animal models has shown that bioelectric stimulation of certain peripheral nerves can successfully regulate glucose levels, opening avenues for improved treatment options for type 2 diabetes.

Around 4.3 million individuals have diabetes in the UK alone, and approximately 90% of these individuals have type 2 diabetes mellitus (T2DM). Patients with type 2 diabetes lose normal control of blood sugar levels, resulting in an overload of sugar in the blood, known as poor blood

sugar regulation or glycaemic control. Inappropriate blood sugar regulation is a result of decreased insulin production by the β -cells of the pancreas, accompanied by insulin resistance.

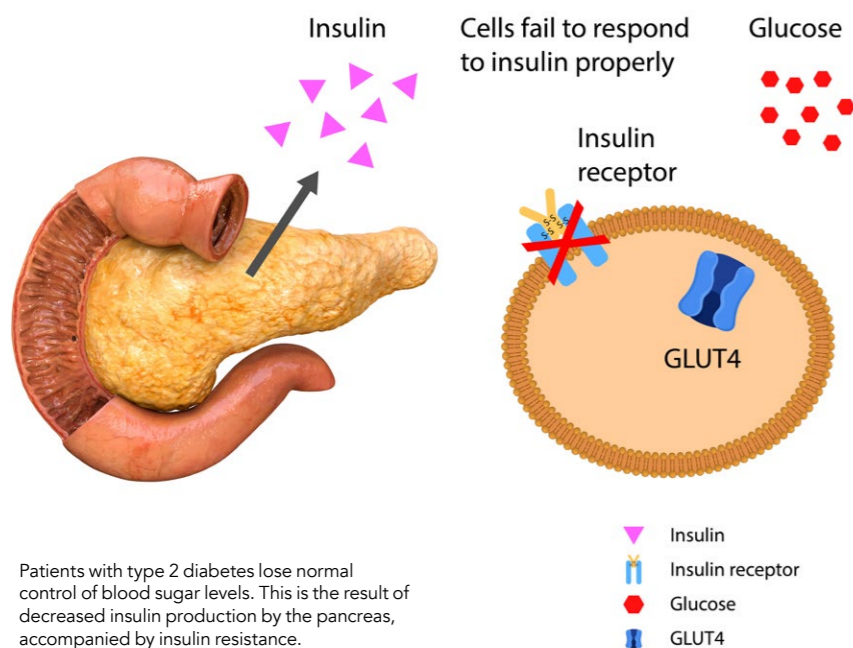
Current treatment modalities of T2DM pose various challenges, despite the

implementation of interventions such as medication, surgery, and dietary changes. For example, approximately 50% of type 2 diabetics do not take medications as prescribed. This is often due to the unwanted side effects of diabetic medications. Even the treatment options – GLP-1 receptor agonists – which improve glycaemic control are linked to kidney injury and severe nausea. Adherence to GLP-1 receptor agonist therapy is also a continuing problem, even with once-weekly injections. The urgent need for better and more effective treatments is an ongoing challenge in the research industry.

Dr Jonathan Waataja of ReShape Lifesciences in California, USA and colleagues have focused their research on the treatment of diabetes using a technique called neuromodulation. Neuromodulation works by electrically stimulating nerves to induce a natural biological response. It can also be achieved by delivering targeted pharmacological medicines in a low dose. What is powerful about this technique is its ability to directly target specific nerves that may be involved in a condition. Leveraging the fact that the vagus nerve activity impacts pancreatic insulin release, Waataja and colleagues have recognised it as a potential target for treating T2DM, one that could benefit from this neuromodulation technique.

TARGETING THE VAGUS NERVE

The vagus nerve carries information from the brain to various organs through its branches and plays a crucial role in regulating involuntary bodily functions, notably blood glucose regulation. It



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achieves this by supplying nerves to the liver and pancreas. This process is called innervation. Numerous researchers have attempted to stimulate the vagus nerve or its branches, but the majority have failed to enhance glucose regulation. Waataja and colleagues chose a slightly different strategy – using a combined neuromodulation approach on the vagus nerve, they investigated the impact on plasma glucose levels. Essentially, the researchers have discovered a novel bioelectric modulation technique for improving blood sugar control, which involves targeting the vagus nerve in two locations instead of just one.

THE BIOELECTRIC NEUROMODULATION DEVICE

Given that the vagus nerve and its branches play a role in regulating various organ systems involved in blood glucose control, it may be necessary to electrically manipulate multiple branches to achieve the best results in lowering blood glucose. This idea inspired the researchers to investigate the effects of

electrically stimulating the vagus nerve at multiple sites, with multiple frequencies. This simultaneous neuromodulation was an alternative method that had not been previously attempted.

In their recent study, Waataja and colleagues managed to stimulate one branch of the vagus nerve, called the celiac branch (innervating the pancreas), while simultaneously blocking another – the hepatic branch, which supplies the

Neuromodulation works by electrically stimulating nerves to induce a natural biological response.

liver. The blockage of the hepatic branch was achieved using a reversible high frequency alternating current.

To evaluate the effectiveness of the technology, the research team tested this device on two different animal models: obese rats and glucose-intolerant swine. Swine have metabolic organ structure and vagus nerve size similar to humans, making them an excellent

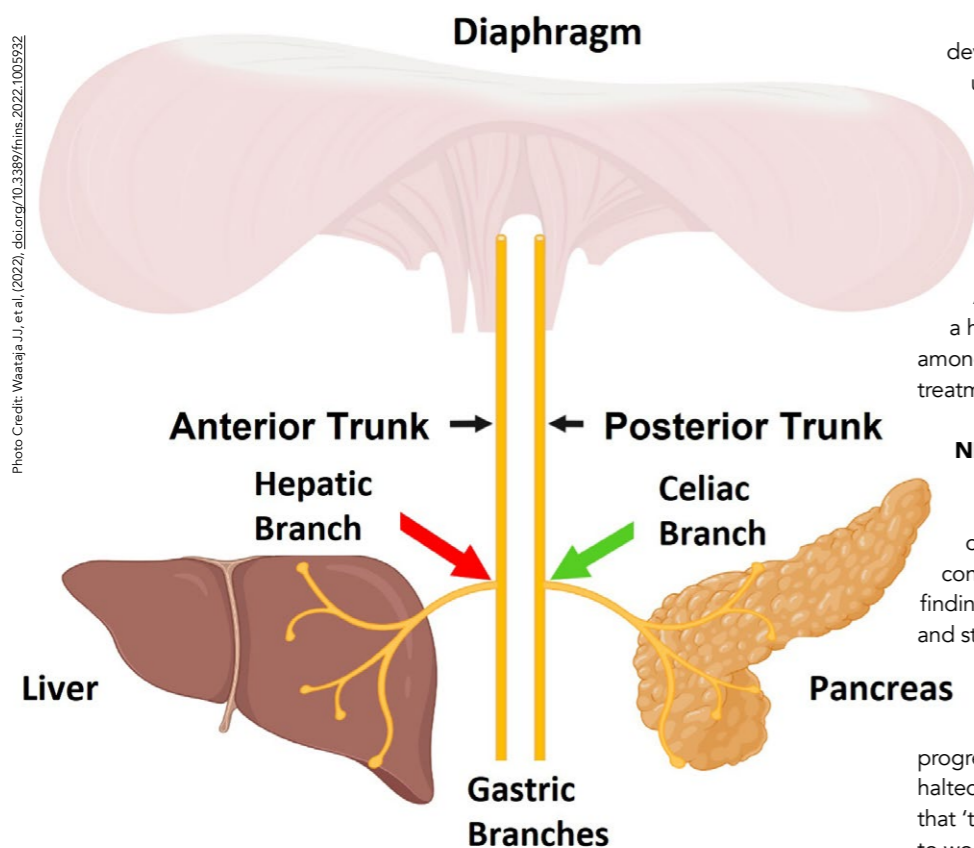
human-like model for testing vagus nerve bioelectronic therapy.

In both models, the celiac and hepatic branches of the vagus nerve were isolated in anaesthetised animals and a device called the neuroregulator was used to administer electrical current to the isolated nerves. Nerve communication along the hepatic branch was blocked with a 5,000 Hz alternating current pulse, whereas the celiac branch was stimulated

at 1 Hz. An hour after the rats were fed, a blood sample was taken to measure blood glucose levels. In the swine models, the neuroregulator was surgically implanted to administer the bioelectric modulation and the nerves were removed later to examine. A special analysis allowed the comparison of results between the species.

THE EFFECT OF BIOELECTRIC ACTIVITY ON BLOOD GLUCOSE LEVELS

Waataja and colleagues discovered that this approach helps improve blood



The vagus nerve consists of two major trunks, the anterior and posterior. The pancreas is primarily innervated by the celiac branch which stems from the posterior vagal trunk. The liver is innervated by the hepatic branch which stems from the anterior vagal trunk. The aim of this study was to apply stimulation to celiac fibres (green arrow) and apply bioelectric current-induced blockade to hepatic fibres (red arrow).

sugar control after meals and during fasting, both of which are crucial for reducing complications in diabetic individuals. By blocking the hepatic vagus branch and exciting the celiac branch, blood glucose performance

The researchers found that the simultaneous blocking and stimulating of the vagal nerve branches increased blood sugar control five minutes after a glucose spike occurred. This means that neuromodulation was found to be most

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was improved in the rats that were tested. The same treatment also resulted in better glycaemic control in the swine model. This study also showed that the effects of the nerve treatment were safe and reversible. Remarkably, this is one of the pioneering studies to successfully increase glycaemic control by modifying nerve activity using two different patterns applied to two distinct targets.

useful when timed at the beginning of a meal. Bioelectric current could be applied to the necessary nerves, just at the onset of a meal, thus reducing the amount of glucose that ends up in the bloodstream.

The team surveyed the sentiment of patients to receiving this type of treatment. Responses from this market research survey indicated that there is interest in using a neuromodulation

device, especially for those currently using lifestyle interventions, such as diet and exercise, to manage T2DM. Over 80% of those surveyed, who are in the early stages of the disease stated they would consider an implant of a neuromodulation device. Analysis of the responses indicate a high probability of adoption among clinicians and patients as a viable treatment option.

NEUROMODULATION – SCOPE AND FUTURE
The early stages of diabetes offer a window into reversing the condition. One particularly interesting finding from this research is that block and stimulation are also effective in these earlier stages. For some individuals, this offers hope that their diabetes condition would not progress any further and may in fact be halted. The research team commented that ‘the system would have the ability to work with AI and machine learning to optimise the vast parameter set involved with multisite, multifrequency vagus branch neuromodulation’. This means that artificial intelligence tools could learn how to master the complex range of inputs involved in stimulating and blocking different nerve sites at the same time. This way, the optimal glucose plasma levels could be managed quickly and effectively.

The results from the animal models demonstrate that a combined neuromodulation approach involving exciting one nerve branch and blocking another improves glucose control, thus providing hope to future patients with type 2 diabetes following the development of an implantable device. The researchers are optimistic that these results can be transferred to human studies.

Waataja and colleagues’ research has rekindled the hope that an effective type 2 treatment could be on the horizon – one with fewer side effects and, possibly, more likelihood of adherence than the existing treatments. The features of this technology are highly adaptable, providing an aspiration for tailored treatment and a potentially different therapeutic experience to treat T2DM.



Behind the Research

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Research Objectives

The research team uses a bioelectronic device comprising targeted dual vagus neuromodulation to demonstrate enhanced glycaemic control in animal models.

Detail

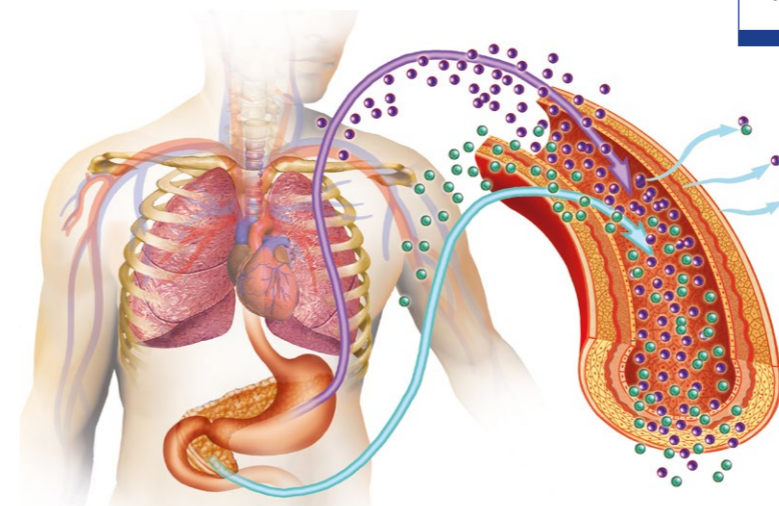
Bio
Dr Waataja received his PhD in neuroscience at the University of Minnesota investigating cellular mechanisms of synaptic degeneration. Following a post-doctoral fellowship in chronic pain and spinal cord electrophysiology, he joined ReShape Lifesciences to pursue research into vagus neuromodulation as a treatment for metabolic diseases such as type 2 diabetes.

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Competing interest statement
Jonathan Waataja and Raj Nihalani are employees of ReShape Lifesciences Inc., the company developing the technology in the manuscript. The other co-authors belong to different academic institutions and do not receive a compensation from ReShape Lifesciences Inc.



References

Waataja, JJ, et al, (2022) Use of a bio-electronic device comprising of targeted dual neuromodulation of the hepatic and celiac vagal branches demonstrated enhanced glycaemic control in a type 2 diabetic rat model as well as in an Alloxan treated swine model. *Frontiers in Neuroscience*, 16, 1005932. doi.org/10.3389/fnins.2022.1005932

Personal Response

How likely are you to see similar effects in humans as in these animal studies?

// We believe the results from this study indicate that there will be similar effects in humans. The translation of effect from a rodent model of type 2 diabetes to a diabetic swine model demonstrates conserved inter-species effects. Treatments of disease that are effective in swine, including GLP-1 receptor agonists, typically predict efficacy in humans. //

What are the long-term effects you hope to see in diabetes patients if they were to use a neuromodulation implant?

// If we can draw a parallel from similar neuromodulation research, we hope to see a decreased use of medication and delaying, or preventing, the need for injectable insulin therapy. Similar neuromodulation techniques targeting the vagus nerve in humans have demonstrated that after three years of therapy, many subjects decreased or stopped diabetic medication. No subjects in the trial progressed to the requirement of insulin therapy. In animal tests, we have observed superior outcomes with our dual-pattern approach compared to what was used in the clinical trial. //

