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REVIEW ARTICLE

IMPLANTABLE INSULIN STIMULATOR

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ABSTRACT

Diabetes is one of the major diseases affecting people all over the world irrespective of the age group. It is mainly classified into 2 types: type 1 and type 2. In type 1 diabetes insulin is not secreted by the pancreas, whereas in type 2 diabetes the cells fail to use the insulin that has been secreted. This proposed stimulator is for type-1 diabetes. It will have a sensor which senses the blood glucose level. In case of high level of glucose the trigger circuit is activated that will stimulate the pancreas to secrete insulin into blood. A timer attached will control the time for which the stimulation has to be given. This whole circuitry is powered by battery. All these set up can be placed in a case similar to the pacemaker. This procedure needs a surgery for the implant and eradicates the continuous injection of insulin to the patient. Thus whenever the blood glucose level goes higher than a preset value, the sensor senses immediately and stimulates the pancreas to secrete insulin and have sufficient adaptability to various metabolic needs due to stress, illness, and exercise and food habits. Thus the normal glucose level in blood is maintained.

INTRODUCTION

Diabetes mellitus is a lifelong condition that can be controlled with lifestyle adjustments and medical treatments. Keeping blood sugar levels under control can prevent or minimize complications. Insulin treatment is one component of a diabetes treatment plan for people with type 1 diabetes (http:// www. uptodate. com/contents/diabetes-mellitus-type-1-insulin-treatment-beyond-the-basics). Insulin treatment replaces or supplements the body's own insulin, restoring normal or near-normal blood sugar levels. Many different types of insulin treatment can successfully control blood sugar levels; the best option depends upon a variety of individual factors. With a little extra planning, people with diabetes who take insulin can lead a full life and keep their blood sugar under control (http:// www. uptodate. com/contents/diabetes-mellitus-type-1-insulin-treatment-beyond-the-basics).

Insulin production

Insulin is a hormone that is exclusively produced by pancreatic beta cells. Beta cells are located in the pancreas in clusters known as the islets of Langerhans (www.betacell.org/ content/articleview/article_id/1/page/2/glossary/0/). Insulin is a small protein and is produced as part of a larger protein to ensure it folds properly.

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In the protein assembly of insulin, the messenger RNA transcript is translated into an inactive protein called preproinsulin (www.betacell.org/ content/ articleview/ article_id/1/page/2/glossary/0/). Preproinsulin contains an amino-terminal signal sequence that is required in order for the precursor hormone to pass through the membrane of the endoplasmic reticulum (ER) for post-translational processing. The post-translational processing clips away those portions not needed for the bioactive hormone. Upon entering the ER, the preproinsulin signal sequence, now useless, is proteolytically removed to form proinsulin. Once the post-translational formation of three vital disulfide bonds occurs, specific peptidases cleave proinsulin. The final product of the biosynthesis is mature and active insulin. Finally, insulin is packaged and stored in secretory granules, which accumulate in the cytoplasm, until release is triggered (www.betacell.org/ content/ articleview/ article_id/ 1/page/2/glossary/0/).

Insulin secretion

The process by which insulin is released from beta cells, in response to changes in blood glucose concentration, is a complex and interesting mechanism that illustrates the intricate nature of insulin regulation. Type 2 glucose transporters (GLUT2) mediate the entry of glucose into beta cell (Fig.2). As the raw fuel for glycolysis, the universal energy-producing pathway, glucose is phosphorylated by the rate-limiting enzyme glucokinase. This modified glucose becomes effectively trapped within the beta cells and is further

metabolized to create ATP, the central energy molecule (www.betacell.org/ content/ articleview/ article_id/ 1/page/2/glossary/0/). The increased ATP: ADP ratio causes the ATP-gated potassium channels in the cellular membrane to close up, preventing potassium ions from being shunted across the cell membrane. The ensuing rise in positive charge inside the cell, due to the increased concentration of potassium ions, leads to depolarization of the cell. The net effect is the activation of voltage-gated calcium channels, which transport calcium ions into the cell.

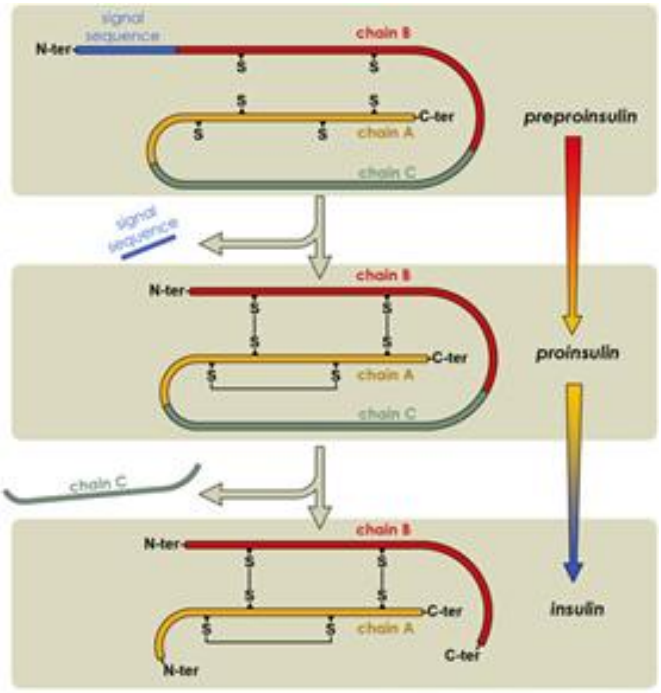

Fig. 1. Insulin synthesis

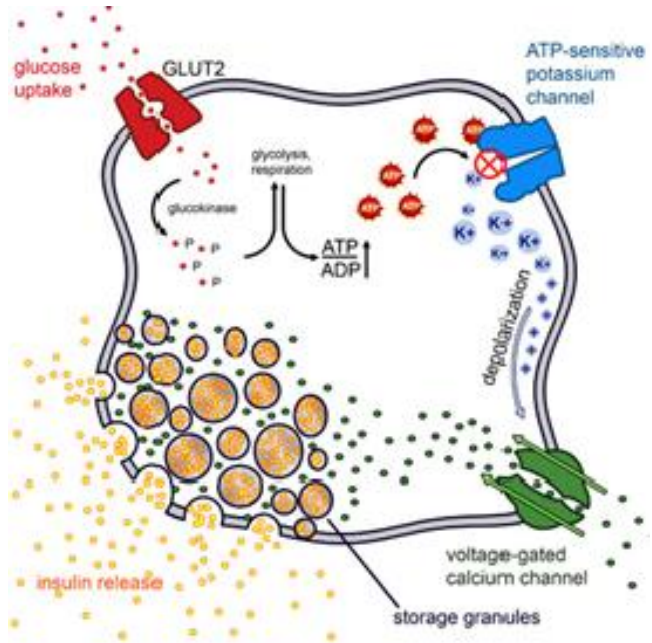

Fig. 2. Insulin secretion

The brisk increase in intracellular calcium concentrations triggers export of the insulin-storing granules by a process known as exocytosis. The ultimate result is the export of insulin from beta cells and its diffusion into nearby blood vessels. Extensive vascular capacity of surrounding pancreatic islets ensures the prompt diffusion of insulin (and glucose) between beta cells and blood vessels. In the proposed system the stimulation can be brought about by using pulses that is given by the trigger circuit. This will cause corresponding polarization and depolarization to bring about effective insulin secretion.

Insulin to action

Insulin molecules circulate throughout the blood stream until they bind to their associated (insulin) receptors. The insulin receptors promote the uptake of glucose into various tissues that contain type 4 glucose transporters (GLUT4). The initial binding of insulin to its receptor initiates a signal transduction cascade that communicates the message delivered by insulin: remove glucose from blood plasma. Among the wide array of cellular responses resulting from insulin activation, the key step in glucose metabolism is the immediate activation and increased levels of GLUT4 glucose transporters. By the facilitative transport of glucose into the cells, the glucose transporters effectively remove glucose from the blood stream. Insulin binding results in changes in the activities and concentrations of intracellular enzymes such as GLUT4. These changes can last from minutes to hours.

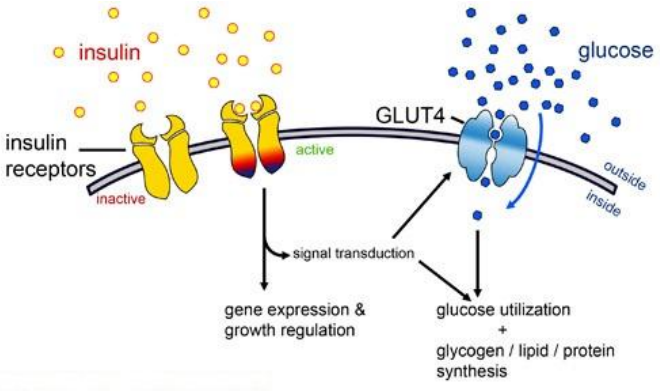

Fig.3. Action of Insulin

The nervous system

The nervous system is made up of central nervous system (CNS) and the peripheral nervous system (PNS). The autonomic nervous system (ANS or visceral nervous system or involuntary nervous system) is the part of the peripheral nervous system that acts as a control system, functioning largely below the level of consciousness, and controls visceral functions. The ANS is classically divided into two subsystems: the parasympathetic nervous system (PSNS) and sympathetic nervous system (SNS) which operate independently in some functions and interact co-operatively in others. They have their own effects on the pancreatic system.

- **Sympathetic:** decreases insulin secretion from beta cells and increases glucagon secretion from alpha cells.
- **Parasympathetic:** increases secretion of both insulin and glucagon.

Innervations

The viscera are mainly innervated parasympathetic ally by the vagus nerve and sympathetically by the splanchnic nerves. The sensory part of the latter reaches the spinal column at certain spinal segments. Pain in any viscera is perceived as referred pain, more specifically pain from the dermatome corresponding to the spinal segment (Moore and Agur, 2002). For the pancreas the nerves responsible are vagus nerve and the thoracic splanchnic nerve and the corresponding spinal cord regions are T8 and T9. Thus the stimulator placement can be determined accordingly.

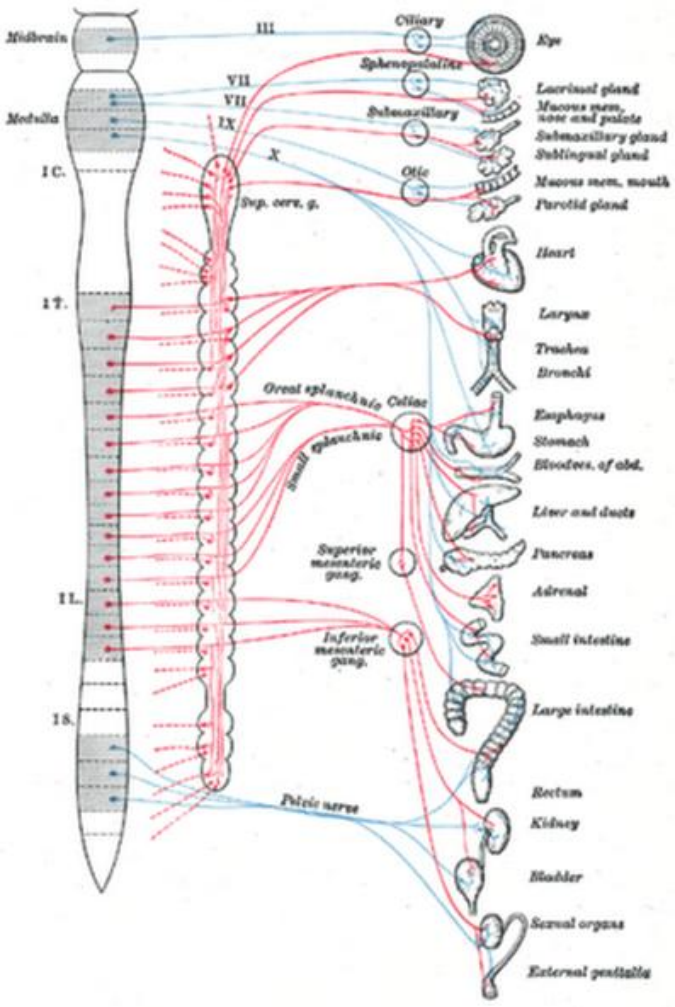

Fig.4. Autonomic nervous system showing splanchnic nerves in middleand the vagus nerve as "X" in blue. The heart and organs below in list to right are regarded as viscera (http://www.daviddarling.info/encyclopedia/A/autonomic_nervous_system.html)

Implantable insulin stimulator

The complete stimulator set up will have the following components:

- Battery – Lithium ion.
- Glucose sensor.
- Needle electrode.
- Pulse generator with timer to set the rate.
- Titanium or glass case.

A.Flowchart

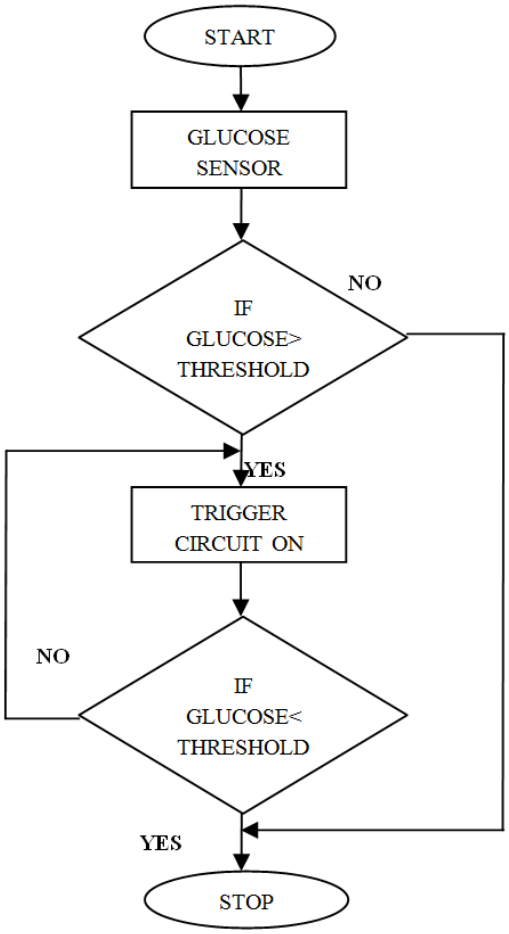

Fig. 5. Flowchart of the proposed system

Thus the glucose sensor senses the level of glucose and checks for the threshold level. If the level is greater than the threshold then the trigger circuit will turn on until the glucose level falls below the threshold. In other case if the threshold level is maintained the trigger circuit is maintained in off condition itself.

B. Working

- This stimulator is placed near the nerve that goes to the pancreas with the needle electrode in contact with the nerve.
- The blood glucose level is sensed by the sensor.
- When the glucose level goes above normal value the pulse generator is triggered.
- This will cause a stimulation that will run down the nerve that is going for pancreas and will cause it to produce insulin.

- This will be drained into blood and thus the glucose level will be brought down by the action of insulin.

Conclusion

Thus this implantable stimulator can be used to maintain the blood glucose level by stimulating the release of insulin eradicating the need of injecting insulin and also it limits the cost of treatment than the usual procedure.

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