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Mini-Review

Nano Particles for Insulin Delivery to Control Diabetes Mellitus

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Abstract

Nanoparticles have superior properties due to their size, volume and charge. The increased surface area enables the nanoparticles to function effectively in the delivery of biochemical substances. When insulin is coated with certain nanoparticles like gold nanoparticles or polylactate nanoparticles their bioactivity became more adjustable. Comparing to free insulin the activity is three times greater for Insulin-Polylactate nanoparticles and Insulin-gold nanoparticles. The coating is found to prevent the fast degradation by the insulin degrading enzyme. This paper explores the applications of nanoparticles for the insulin delivery to control diabetes mellitus, a metabolic disorder.

Introduction

Normally pancreatic beta cells produce insulin in presence of carbohydrates or sugar. When our body lacks the ability to regulate body glucose by releasing sufficient or releases no insulin then we suffer from Diabetes [1].

There 2 types of diabetes type 1 diabetes and type 2 diabetes. Type 1 is caused due to lack or production of low amount of insulin [2]. Insulin replacement therapy is used to treat this. But this method should be employed life long. And type 2 diabetes is caused due to the lack of proper working insulin due lack of sensitivity of liver [3].

Diabetes is a very dangerous disease. It is also expensive to cure it anywhere. Initially diet control and exercise are used to treat the disease. When these methods prove futile then only medicines are employed [4-6].

There are several ways to consume drugs. The most widely used way to deliver the drug is through injections. Many patients refrain from injecting insulin as it causes bruises and requires frequent injections. Orally these drugs have to be taken in large amounts as in small amounts they are not effective, causing a lot of side effects in patients. So many patients refuse to take insulin through oral pathway. Also protein structure of insulin is destroyed by enzymes and less absorption takes place through this pathway.

Both type 1 and type 2 diabetes can be treated through oral pathway to deliver insulin. Oral pathway is the most comfortable way. To prevent the problems from occurring insulin is delivered efficiently in a steady manner using nano carriers [10-11]. After several experiments in mice and rats, ways to deliver insulin using nanoparticles have been found through oral and subcutaneous injections. This method has shown increase in the medicine's effectiveness, its absorption and the insulin's protein structure has been well protected. But this method also has cons.

INS-GNP Nanoparticles

For an ideal insulin solution, it is necessary that it possesses a long effective period. This avoids the problem of forgetting insulin injections and the inconvenience of periodical injections. To enable and introduce such features special insulin plus nanoparticles like INS-GNPs are employed. INS-GNPs are insulin coated with gold nanoparticles. They effectively release, enhance and protect insulin from degradation. The best and the most preferred method of delivery of insulin is through oral pathway.

PLA-PEG and PHBHHx Nanoparticles

Similarly, PLA-PEG NPs is effective for more than 7 days. Unlike common nanoparticles they are non toxic. Studies conducted show that nanoparticles introduced insulin worked 3 times better than the normal injected insulin. Experiments done on laboratory bred mice show that injection of 50nm INS-GNPs is more effective than 20 and 70nm INS-GNPs. In experimental conditions like *in vitro*, PHBHHx NPs show long term insulin effect and is efficient up to 90%. As the insulin is well attached to the nanoparticle and

because of INS-PLC44. Taking a batch of diabetic rats and injecting them with INS-PLC-NPs gave back highly effective, stable, efficient result up to three days

Glucose Responsive Insulin Delivery

So, it showed a better effect than free insulin. We can make the body release insulin by injecting substances that act as a stimuli for release of insulin. This way of controlling the glucose level of patients is called glucose-responsive insulin delivery system method. In this method, pancreatic β-cells release insulin in response to high glucose level in patients. The method uses various glucose sensitive substances which are fitted with insulin. These substances change their structure and lead to release of insulin when the glucose level in the environment gets beyond a certain point.

The Different Systems and Their Mechanism of Action

There are different ways based on the type of system used, that is glucose oxidase-based system, glucose binding protein-based system, glucose binding molecule-based system and modified insulin-based system. The glucose-responsive systems employ glucose oxidase to lower the blood glucose. Glucose oxidase has high sensitivity towards glucose. In presence of glucose oxidase glucose is converted to gluconic acid and hydrogen peroxide. A hydrogen ion is released from gluconic acid makes the medium acidic. It reduces the pH of the medium. This acidic medium reacts with the hydrogen peroxide which causes the walls of the substance to break leading to release of insulin.

For example Qi *et al* reported microcapsules composed of glutaraldehyde cross-linked glucose oxidase (GOD) and hemoglobin layer by layer. As the pH of the medium decreases on the production of gluconic acid, the capsule dissolve and releases insulin. Even mesoporous silica nano-device capped with cyclodextrin-modified-glucose oxidase (CD-GOD) can also be used to control glucose levels.

Studies have developed a glucose-responsive system, nanocapsules of GOD and CAT are introduced with insulin. A self-regulating valve system is used here. Insulin is released only when required. Like explained above glucose is converted into gluconic acid. The amino acids are protonated by the gluconic acid. This in turn increases the charge of the matrix. This causes the release of insulin. When hydrogen peroxide accumulates, GOD is inhibited and abnormal growth can happen.

Conclusion

The experiments show that for controlling the high blood glucose levels insulin-gold nanoparticles are three times efficient than the traditional insulin injections which badly affect the quality of life of the patient. It was shown that Polylacticacid-Polyethyleneglycol nanoparticles (PLA-PEG NPs), and Poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) nanoparticles (PHBHHxNPs) can be effectively used for optimum drug release of insulin. Insulin-Polylactate nanoparticles also are highly useful for the prolonged release of insulin in the living system. Cyclodextrin-modified-glucose oxidase can be widely used as biosensors for glucose due to the electrochemical oxidation of hydrogen peroxide in the enzymatic reaction.

Bibliography

1. Zhang, P., Zhang, X. Z., Brown, J., Vistisen, D., Sicree, R., Shaw, J., *et al.* (2010). Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res ClinPract., 87*(3), 293-301.

2. Tuomilehto, J., Lindstrom, J., Eriksson, J. G., Valle, T. T., Hamalainen, H., Ilanne-Parikka, P., *et al.* (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med., 344*(18), 1343-1350.

3. American Diabetes A (2014). Standards of medical care in diabetes-2014. *Diabetes Care, 37* Suppl 1, S14-80.

4. Peng, Q., Sun, X., Gong, T., Wu, C. Y., Zhang, T., Tan, J., *et al.* (2013). Injectable and biodegradable thermosensitive hydrogels loaded with PHBHHx nanoparticles for the sustained and controlled release of insulin. *Acta Biomater, 9*(2), 5063-5069.

5. Lee, K. C., Chen, W. J., Chen, Y. C. (2017). Using dextran-encapsulated gold nanoparticles as insulin carriers to prolong insulin activity. *Nanomedicine (Lond)., 12*(15), 1823-1834.

6. Chen, M. C., Sonaje, K., Chen, K. J. & Sung, H. W. (2011). A review of the prospects for polymeric nanoparticle platforms in oral insulin delivery. *Biomaterials, 32*(36), 9826-9838.