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Review

Applying emerging technologies to improve diabetes treatment

Jiaojiao Yu[a,b], Caifeng Sun[a,b], Yuli Wei[a,b], Chaoying Wang[a,b], Brijesh Dave[c], Fei Cao[a,b], Liandong Hu[a,b,⁎]

[a] School of Pharmaceutical Sciences, Hebei University, Baoding, China
[b] Key Laboratory of Pharmaceutical Quality Control of Hebei Province, Hebei University, Baoding, China
[c] Amerigen pharmaceuticals Inc., USA

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ABSTRACT

Insulin, as the most important drug for the treatment of diabetes, can effectively control the blood glucose concentration in humans. Due to its instability, short half-life, easy denaturation and side effects, the administration way of insulin are limited to subcutaneous injection accompany with poor glucose control and low patient compliance. In recent years, emerging insulin delivery systems have been developed in diabetes research. In this review, a variety of stimuli-responsive insulin delivery systems with their response mechanism and regulation principle are described. Further, the introduction of stem cell transplantation and mobile application based delivery technologies are prudent for the diabetes treatment. This article also discusses the advantages and limitations of current strategies, along with the opportunities and challenges for future insulin therapy.

1. Introduction

Diabetes mellitus is the most serious health epidemic in the world hyperglycemia. Diabetes can be divided into type 1 and type 2, which is mainly due to insufficient insulin secretion caused by islet cells damage, resulting in high blood glucose levels (BGL) in the body [1–3]. The number of people suffering from diabetes worldwide is rising rapidly. About 422 million adults were living with diabetes in 2014, compared to 108 million in 1980.

Insulin is a 51 amino acid polypeptide discovered by Banting and Best [4] in 1922 (Fig. 1) [5]. Since its discovery, the properties of insulin have been widely studied. However, since insulin is not easily penetrated by biofilms and destroyed in the gastrointestinal tract by digestive enzymes, it has been administered mainly by subcutaneous injection, which is not only inconvenient, but also causes physical and psychological pain to the patient and accompanies by a variety of adverse reactions. The hard dose adjustment brings the risk of hypoglycemia during the long-term administration, hampering the patient's quality of life [6].

Due to the drawbacks of conventional insulin therapy, researchers are committed to the development of new routes of insulin administration. In recent years, smart insulin delivery systems with stimuli-responsive functions can release insulin when the blood glucose concentration increases, which has attracted more and more attention.

Stimuli-triggered insulin delivery can be typically classified into two types, physiological stimuli including pH, redox potential, enzymatic activities and glucose concentration and external stimuli such as temperature, light, electric field, magnetic field and mechanical force. In addition, the advancement of stem cell transplantation and mobile apps [7] has been developed to improve diabetes treatment. This article reviews emerging technologies mentioned above to improve diabetes treatment (Fig. 2).

2. Physiological stimuli-triggered delivery

2.1. pH-sensitive insulin delivery

A large part of the drug release systems are triggered by pH dependent direct or indirect physiological stimuli. The pH-sensitive system uses pH-sensitive polymers to produce a physical and chemical transition during the alteration of pH in the surrounding medium, the changes include the hydrogel swelling, vesicle cracking, micelle dissociation. membrane fusion and disruption, bond cleavage and so on [3]. In recent years, pH-sensitive polymers have been widely used to make insulin delivery systems to maintain glucose levels.

Gao et al. [8] synthesized biodegradable and pH-sensitive carboxymethyl cellulose/poly (acrylic acid) hybrid hydrogels. Insulin-loaded hydrogels were orally administered to streptozotocin-induced diabetic rats, which resulted in a continuous decrease in fasting blood glucose levels within 6 h. Its relative pharmacological availability increased

⁎ Corresponding author at: School of Pharmaceutical Sciences, Hebei University, Baoding, China.
E-mail address: gz1205@126.com (H. Liandong).

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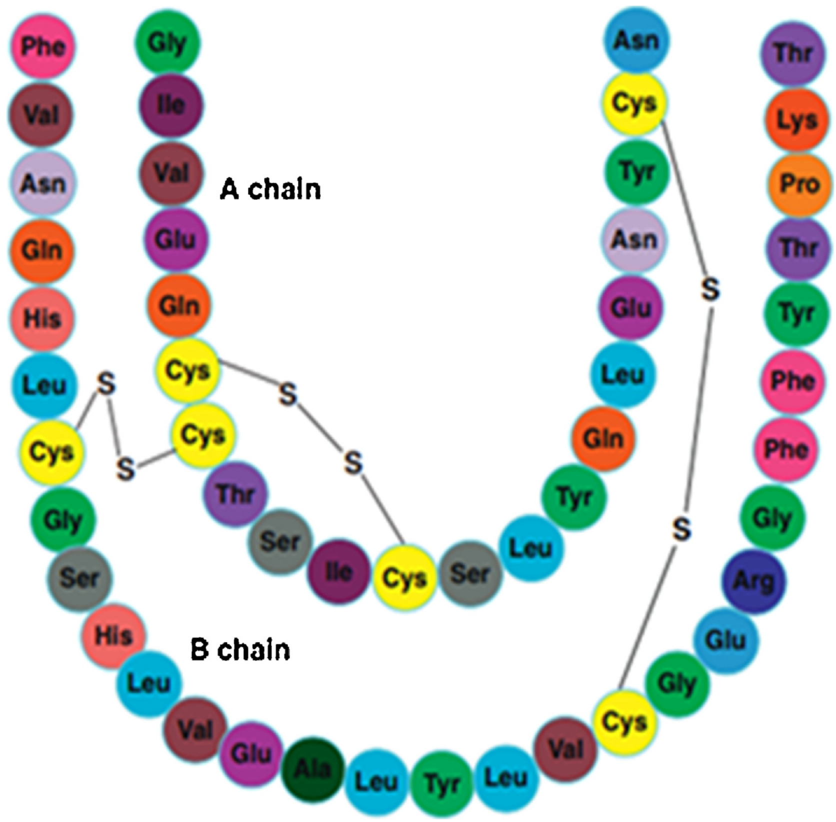

Fig. 1. Structure of insulin. Reproduced with permission from Elsevier, copyright 2012.

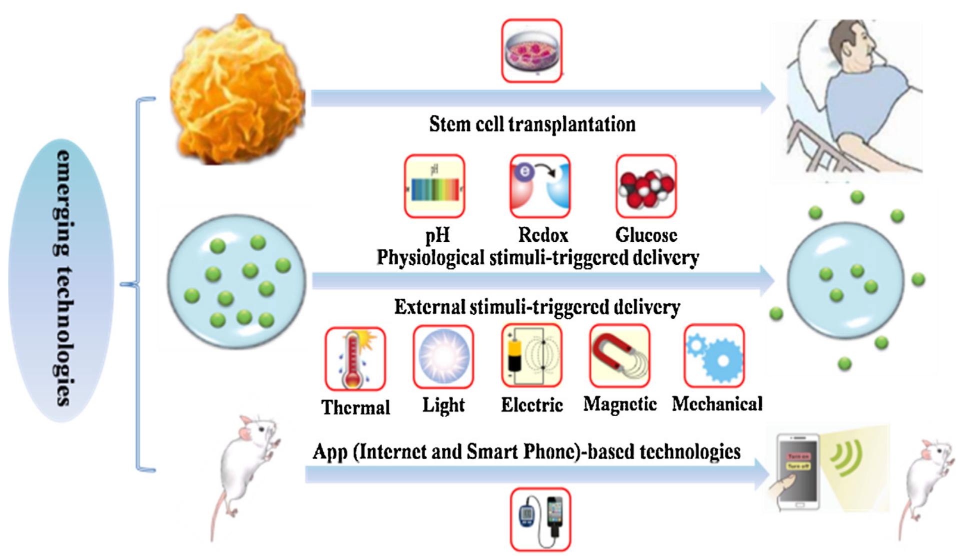

Fig. 2. Emerging technologies to improve diabetes treatment.

more than 10 times compared with oral insulin solution.

The design of a series of new salecan-based pH-sensitive hydrogels was another approach for controlled insulin delivery [9]. Salecan adjusted the water content and water release rate of hydrogels, resulting in a controlled release of insulin. In vitro release experiments demonstrated that the release of insulin from the intelligent system could be regulated by the environmental pH of the release medium. The drug uptake efficiency was depicted vividly (Fig. 3A), as the salecan dose increased from 2.5 (SGA1) to 10 mL (SGA4) respectively, the drug loading efficiency increased from 22.1% to 56.4%. The amount of encapsulated insulin released under gastric conditions (pH 1.2) was relatively low (about 26.1% in 24 h), but increased significantly over 50% in 6 h under intestinal conditions (pH 7.4) (Fig. 3B, C). The UV–vis absorption spectra of standard and released insulin was also illustrated (Fig. 3D). It was found that insulin was released from the hydrogel network in its original form and that the delivery system did not produce detectable impurities. All tests demonstrated that the insulin delivery system was effective in this study and that insulin was not broken throughout the entire process [10].