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Engineering glucose-responsive insulin

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ABSTRACT

People with type 1 or advanced type 2 diabetes are highly dependent on insulin. However, insulin cannot match its function to daily varying blood glucose levels, putting people with diabetes at risk of hypoglycemia. Glucose-responsive insulin is capable of improving blood glucose manipulation and elevating the life quality of people with diabetes. Therefore, enormous endeavors have been devoted to developing glucose-responsive insulin formulations, including glucose-responsive insulin delivery systems and glucose-responsive insulin analogs. In this review, we focus on glucose-responsive insulin analogs, especially three representatives, including phenylboronic acid-mediated, glucose transporter-mediated and lectin-mediated glucose-responsive insulin analogs. Based on the published studies, the opportunities and challenges to engineering glucose-responsive insulin analogs are also discussed.

1. Introduction

Diabetes mellitus, a chronic disease characterized by high blood glucose levels (BGLs) [1], affected about 463 million people worldwide in 2019 [2] and ranked the seventh global cause of death in 2016 [3]. People with type 1 or advanced type 2 diabetes need a lifelong administration of insulin or insulin analogs, combined with self-monitoring of BGLs, healthy diets and regular exercise [4]. However, the complications induced by hyperglycemia and the risk of hypoglycemia are challenging to get rid of, due to the narrow therapeutic index of insulin and the inability of insulin to respond robustly to daily fluctuating BGLs [5–7]. Therefore, the development of insulin therapy that can mimic the function of the β-cell to release insulin in a glucose-dependent manner is urgently demanded to improve the BGLs management outcome.

Up to now, two major strategies, including constructing glucose-responsive insulin delivery systems and formulating insulin analogs, have been widely investigated to render insulin glucose responsiveness [8–11], *via* employing the three major glucose-responsive elements including phenylboronic acid (PBA), glucose-binding protein (such as concanavalin A) and glucose oxidase [12–25]. These compounds are effective in constructing glucose-responsive carriers for insulin delivery. However, issues, considering the metabolism-associated biocompatibility and toxicity of carrier materials, remain to be solved [26,27]. Glucose-responsive insulin analog reformulates insulin in the molecular level without the aid of a carrier material, therefore offering a relatively safer and simpler path to achieve glucose responsiveness. Nonetheless, studies involving glucose-responsive insulin analogs are limited, partially due to various hurdles [9,28–32], such as the susceptible bioactivity of insulin and non-specific binding of the prepared insulin analogs. In this review, the latest advances of glucose-responsive insulin analogs, from labs to industries, have been summarized (Fig. 1). Meanwhile, the opportunities and challenges in this field are also discussed.

2. Glucose-responsive insulin

2.1. PBA-mediated insulin analog

The molecular weight shows a significant influence on the diffusion rate and the consequent half-life of a subcutaneously injected protein drug [33]. For example, hexameric insulin or insulin integrated with a macromolecular protein has longer retention time than monometric insulin. Inspired by this connection between molecular weight and acting time of insulin, in 2005, Markussen and coworkers conjugated both PBA and polyol to a single insulin molecule [33]. In this insulin analog, both PBA and polyol provided binding sites for each other, therefore forming self-assembled long-acting insulin assemblies. When a carbohydrate (like glucose) was added, the insulin assembly was dissembled and released monomeric insulin for fast acting to reduce BGLs.

Recently, Langer, Anderson and coworkers reported several PBA-based insulin analogs with glucose-responsive activity [30]. In this study, four aliphatic chain-containing PBA-modified insulin analogs,

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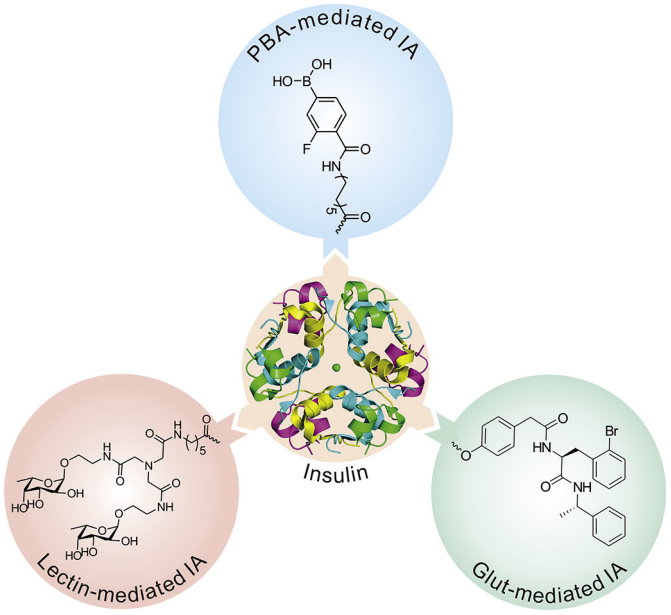

Fig. 1. Schematic of the representative strategies to formulate glucose-responsive insulin analog (IA).

including Ins-PBA-A, Ins-PBA-F, Ins-PBA-N, and Ins-PBA-S, have been prepared (Fig. 2A). The PBA moiety that conjugated to aliphatic domains in the insulin analog could bind to glucose, making the affinity between aliphatic domains and albumin or other hydrophobic components in blood glucose dependent, and consequently endowing the insulin analogs with glucose-dependent half-lives during blood circulation [34,35]. Of note, the incorporated PBA moiety could also bind to diols in glycosylated proteins, which further contributed to glucose responsiveness of the insulin analogs [36]. The glucose-responsive performance and blood glucose regulation ability of these insulin analogs were evaluated in mice with type 1 diabetes. After the BGLs of diabetic mice treated with insulin analogs or native insulin were restored to a normal range (below 200 mg/dL), three intraperitoneal glucose tolerance tests (IPGTTs) were performed (Fig. 2B). The native insulin failed to restore BGLs to the normal range at the first IPGTT. However, both Ins-PBA-F and Ins-PBA-N were able to restore BGLs to the pre-challenge levels even after three IPGTTs. Particularly, Ins-PBA-F exhibited better performance in manipulating blood glucose than Ins-PBA-N, as shown in Fig. 2B. To further explore the glucose dependent activity of Ins-PBA-F, dose-escalated IPGTTs of Ins-PBA-F were conducted in both diabetic and healthy mice, while Ins-LA-C14 (Fig. 2A) and native insulin were used as controls. Ins-PBA-F showed higher glucose responsiveness index and less hypoglycemia index than Ins-LA-C14 and native insulin (Fig. 2C-D). By virtue of the binding of aliphatic domain to the hydrophobic domain of serum or other blood component and the reversible glucose binding ability of PBA, prolonged and glucose-dependent glycemic control of Ins-PBA-F have been achieved in the diabetic mice, providing us a route for formulating a long-acting glucose-responsive insulin analog. Before its clinical trial, further work on biocompatibility and toxicity needs to be performed considering the difference across species and the non-specific binding of PBA to various types of diols.

2.2. Glucose transporter-mediated insulin analog

Recently, Gu and coworkers proposed a strategy to leverage glucose transporter (Glut) to construct a glucose-responsive insulin delivery

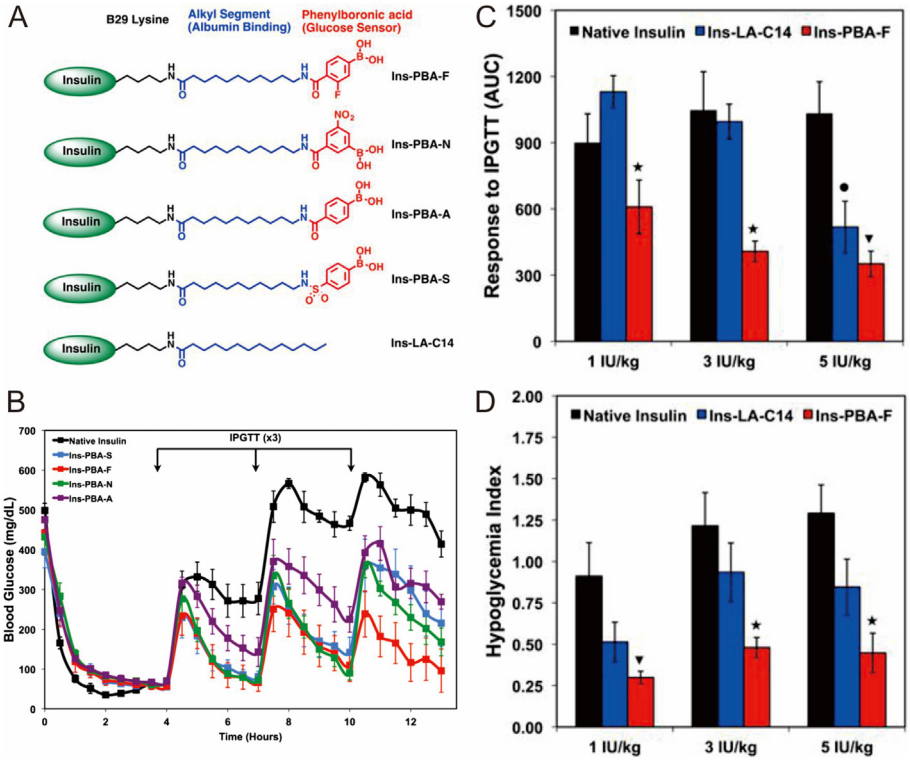

Fig. 2. PBA-mediated glucose-responsive insulin analogs. (A) The structure schemes of the four types of PBA-modified insulin derivatives and the long-acting insulin Ins-LA-C14, which has the same structure as commercially used long-acting insulin detemir. (B) The BGLs of diabetic mice after the administration of different insulin derivatives. The diabetic mice were injected with different insulin derivatives at a dose of 5 IU/kg at 0 h and then three IPGTTs were performed at 4, 7, and 10 h, respectively. (C) The responsiveness of insulin derivatives. The data were calculated according to the blood glucose curve area between 3 h and 6 h after insulin administration in diabetic mice. (D) The hypoglycemia index of healthy mice after the treatment with different insulin derivatives at various doses. Here, the hypoglycemia indexes were calculated by the difference between initial and lowest blood glucose values divided by the time over which the blood glucose drop happened. $^{\star}P < .05$ for Ins-PBA-F compared with both Ins-LA-C14 and native insulin; $^{\star}P < .05$ for Ins-PBA-F compared with native insulin; $^{\star}P < .05$ for Ins-LA-C14. Reprinted with permission [30]. Copyright 2015, National Academy of Sciences.

system [37]. Glucosamine conjugated insulin (Glc-Insulin) was prepared with the ability to bind to the Glut on the membrane of red blood cell (RBC). Such binding was reversible that Glc-Insulin could be released from the RBC membrane upon high BGLs, mediated by the competitive binding between Glc-Insulin and free glucose in blood to Glut. Gu and coworkers further exploited the concept of competitive binding toward Glut to construct a glucose-responsive insulin analog named *i*-insulin [31]. *i*-Insulin was synthesized *via* conjugating insulin to a Glut inhibitor (Fig. 3A). The Glut inhibitor moiety in *i*-insulin could bind to Glut in a glucose-competitive manner, therefore enabling *i*-insulin to dynamically and reversibly bind to Glut in response to BGLs. Meanwhile, *i*-insulin retained the ability to trigger the clearance of glucose. *In vitro*, *i*-insulin could reversibly bind to erythrocyte ghost, a generally used Glut carrier, and the binding ability was modulated by changing glucose concentration. In type 1 diabetic mice, with one injection, *i*-insulin-treated mice had a prolonged normoglycemia (>10 h) and negligible hypoglycemia as compared to native insulin-treated mice (normoglycemia lasted for <4 h) (Fig. 3B). Importantly, a second *i*-insulin injection further prolonged the normoglycemia time while negligible hypoglycemia was observed (Fig. 3C). This hypoglycemia-mitigating effect was evaluated in healthy mice. Only negligible hypoglycemia was observed in *i*-insulin-treated mice while native insulin injected group showed apparent hypoglycemia (Fig. 3D). Therefore, *i*-insulin has achieved both blood glucose regulation and hypoglycemia mitigation in type 1 diabetic mouse model. Furthermore, another Glut inhibitor, forskolin, was conjugated to native insulin and a new glucose-responsive insulin analog (insulin-F) was formed [38]. Here, the concept of competitive binding between insulin analog and glucose toward Glut was applied to construct glucose-responsive insulin for manipulating glycemia. This strategy offers a new methodology in formulating glucose-responsive insulin associated with both insulin receptor and glucose transporter.

2.3. Lectin-mediated insulin analog

In 2010, Merck & Co., Inc. acquired a startup SmartCells who developed a smart insulin later called MK-2640. MK-2640 is an insulin analog (Fig. 4), in which the insulin is modified with carbohydrate groups to

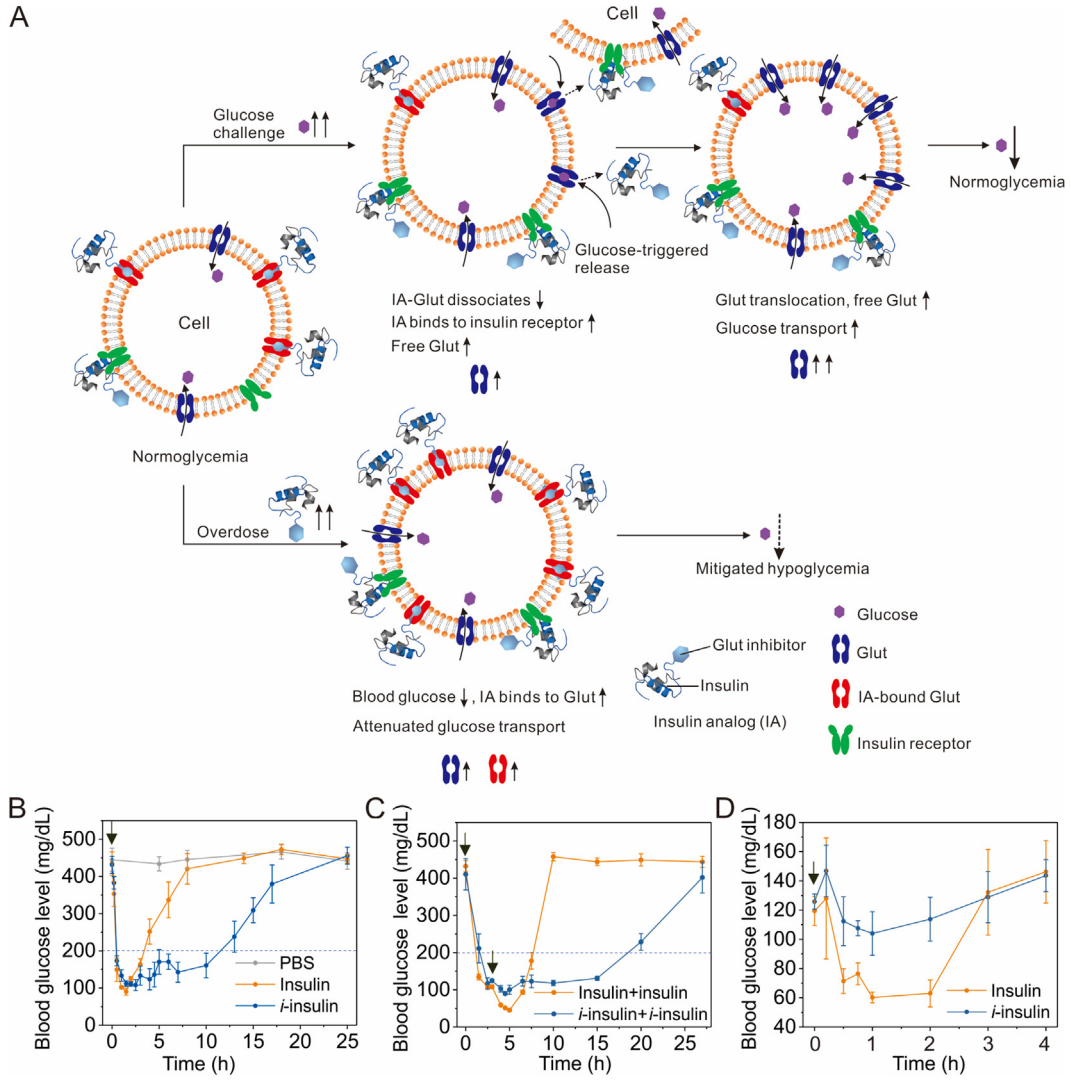

Fig. 3. Glut-mediated glucose-responsive insulin analog. (A) Schematic of insulin analog (*i*-insulin) reducing hyperglycemia and mitigating hypoglycemia. Under normoglycemia, *i*-insulin binds to Glut or insulin receptor, achieving a regular glucose clearance rate. Upon high glucose level, the increased glucose triggers the release of *i*-insulin from insulin analog-Glut complex, leading to elevated *i*-insulin binding to insulin receptors and increased amount of free Glut to transport glucose. As a result, blood glucose clearance is significantly enhanced. Upon overdose of *i*-insulin, more insulin analog-Glut complex is formed, leading to attenuated glucose transport activity of Glut. As a result, the hypoglycemia is mitigated. (B–D) The *in vivo* study of *i*-insulin. (B) the BGLs of type 1 diabetic mice after receiving the treatment of *i*-insulin (6 mg/kg), native insulin (1.5 mg/kg) and PBS respectively. (C) The BGLs of type 1 diabetic mice receiving two consecutive injections. The second injection was performed 3 h after the first injection. The injection dose was 6 mg/kg for *i*-insulin or 1.5 mg/kg for native insulin. (D) The BGLs of healthy mice after injected with *i*-insulin (3 mg/kg) or native insulin (0.75 mg/kg) to induce hypoglycemia. The black arrows indicate the time points of injection. Data are presented as mean ± SD ($n = 5$). Reproduced with permission [31]. Copyright 2019, National Academy of Sciences.

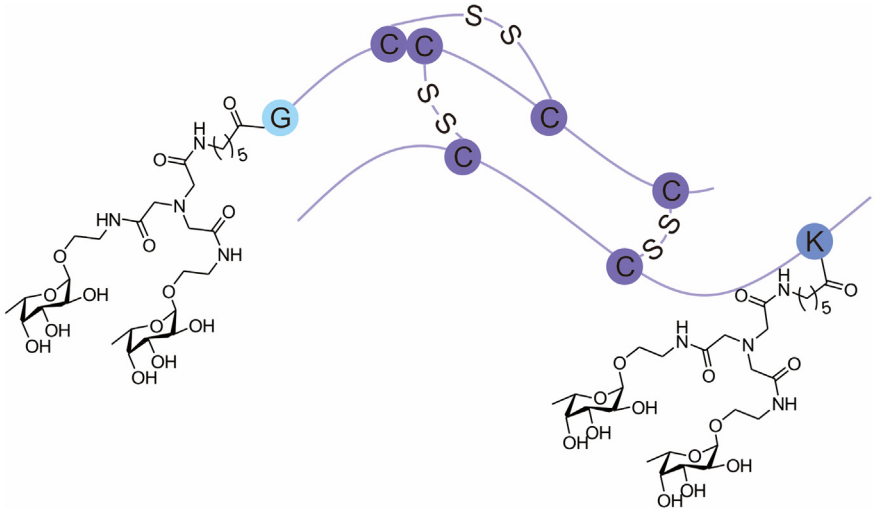

Fig. 4. The schematic of the chemical structure of MK-2640. Here, G, C and K represent Glycine, Cysteine and Lysine respectively.

render insulin with the ability to bind to the lectin receptor mannose receptor C-type 1 (MRC1). The competitive binding between MK-2640 and glucose to MRC1 was exploited to tune the blood clearance rate of MK-2640 [39]. The glucose responsiveness of both MK-2640 and recombinant human insulin (RHI) were evaluated in nondiabetic (ND) and type 1 diabetic (D) minipigs, with α-methylmannose (α-MM) used as a short-term blockade of MK-2640. The addition of α-MM did not affect the pharmacokinetics (PKs) and pharmacodynamics (PDs) of RHI; however, transient hypoglycemia was observed in ND minipigs when MK-2640 was administrated with α-MM, because the clearance of MK-2640 was protracted by the infused α-MM. In the glucose clamp studies in healthy dogs, the clearance of MK-2640 was decreased with stepwise increased glucose concentration, in contrast to that observed in RHI treated group. Although MK-2640 presented effective glucose responsiveness in the minipig and dog studies [32], the results of human trials were not optimistic [40]. In the phase I clinical trial, 36 healthy adults participated in the rising dose study of MK-2640 administration, and 16 patients with type 1 diabetes enrolled in a randomized 2-period crossover test to explore the glucose responsiveness of MK-2640. However, the saturation of MK-2640 clearance through MRC1 receptor and glucose independence of MK-2640 clearance indicated the difficulties in clinical translation [40]. Therefore, in 2016, Merck claimed that the clinical trial failed and ended it. The failure of MK-2640 elaborated the difficulties in clinical translation of new drugs considering the difference between species although exciting preclinical data were obtained. In this field, more efforts should be devoted to the investigation of new designs in clinical trials.

3. Conclusions

The development of glucose-responsive insulin analog, aiming at improving insulin efficacy and reducing side effects, attempts to enhance the health and the quality of life of people with diabetes. To render insulin analog glucose responsiveness, scientists have proposed several strategies from perspectives of pharmacy, biochemistry and engineering. With additional functional moieties modified on insulin, the glucose-dependent binding between functional moieties and corresponding "receptors" associated with proteins and cells improved the blood glucose regulation ability of insulin. For further translation, the issues considering drug activity, binding specificity, and biosafety of insulin analog must be thoroughly investigated. Moreover, the difference between human bodies and animal models also sets a barrier to clinical translation. Nevertheless, previous trials still offer us valuable insights into designing new insulin analogs. Furthermore, the administration method is another aspect needed to be considered during medical treatment. For example, using microneedle patch [41,42], the painless and minimally invasive transdermal drug delivery method, or oral delivery pills could help people with diabetes achieve self-administration in a convenient manner.

Ethical approval and informed consent

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Author contributions

Yi Zeng, Jinqiang Wang and Zhen Gu conceived and designed the manuscript. Yi Zeng wrote the initial manuscript. All authors revised and edited the paper together.

Declaration of competing interest

Prof. Zhen Gu is the co-founder of Zenomics Inc.

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