Smart insulins

Abstract

This review addresses a futuristic frontier of diabetes pharmaco-therapeutics. It describes the current status, and future prospects, of development of smart insulins, i.e., insulins which self-regulate their release, in response to ambient glycaemic levels. This approach helps to minimize the risk of hypoglycaemia, and ensures physiological control. The article discusses the various technical strategies used to create such smart insulin.

Keywords: Diabetes, Pharmaco-therapeutics, Smart insulins.

Introduction

One of the greatest challenges in diabetes praxis today is the risk of hypoglycaemia.\(^1\) This limits our ability to achieve optimal HbA1c without putting our patients at risk of a potentially life threatening situation. Newer insulins have been developed which address this issue.\(^2\) However, physiological replacement of insulins still requires multiple subcutaneous injections, or use of insulin pumps. The risk of hypoglycaemia, though minimal, is not obviated completely.

One approach to resolve this issue has been the development of smart insulins. Smart insulin is defined as a pharmaceutical preparation which contains an inbuilt sensor mechanism to assess ambient glycaemia, and ensures release of insulin based upon this information. It avoids both hypoglycaemia dips and hyperglycaemia peaks, while ensuring euglycaemia. This approach, though currently far from perfection, has the potential to revolutionize insulin therapy.

As long back as 1979, Brownlee and Cerami reported the synthesis of a stable, biologically active glycosylated insulin derivative, combined with a lectin called concavalin A. This synthetic ligand-bound insulin releases active insulin in a quantity proportional to the amount of glucose present.\(^3\) In recent decades, medicine has begun to use other ‘smart sensing’ drugs and devices Cardiac pacemakers, implantable cardiac defibrillators, and closed loop mechanical ventilator devices are examples of such devices.

Smart insulins, too, have experienced active development in the past few years. Well written reviews cover this field in great detail.\(^4,5\) However, newer research has emerged which call for an updated review of the topic. This review outlines such advances, with an emphasis on recently reported breakthroughs.

Conventional Smart Insulins

Protein Binding Ligands

The first work in the field of smart insulin was done using lectins, a family of proteins known to bind reversibly, but avidly and specifically, to carbohydrates. Concavalin A was used to bind to glycosylated insulin, which retained its bioactivity. This insulin ligand complex released insulin upon being stimulated by ambient hyperglycaemia to dissociate.\(^5\) However concerns about immunogenicity of concavalin A as well as glycosylated insulin have led to abandonment of this field of research. No patents have been applied recently for using lectins as a basis for smart insulin.

Bulk Hydrogel Matrix

Bulk hydrogel matrices have been reported to function as chemically controlled closed-loop insulin delivery devices.\(^6\) Most of them are based upon glucose oxidase as a glucose sensing mechanism. They
swell in response to hyperglycaemia, and this stimulates entrapped glucose to break down and activate insulin, which in turn corrects the hyperglycaemia. However, earlier attempts at utilizing hydrogels were limited by the slow response time of these materials. This led to an unacceptably long delay in release of insulin in response to hyperglycaemia, and a risk of hyperglycaemia because of prolonged insulin release under normoglycaemic conditions.

**Phenyl Boronic Acid**

Phenylboronic acid (PBA) has also been used as a glucose -sensing material in smart insulins. When PBA is immobilized in a hydrogel, addition of glucose creates a negative charge in the gel, thus allowing water to diffuse in and create an increase in volume. This method can be used to create a gluco-responsive insulin. Later authors have described PBA based microgels which shrink in response to exposure to hyperglycaemia. The need for alkaline pH, however, severely limits the utility of PBA based smart insulins. Especially in the unwanted event of an episode of diabetic ketoacidosis, such smart insulin may cease to function.

**Nano-Technology Based Smart Insulins**

**Nano-Membranes**

Multifunctional, nano- composite membranes have been developed which are able to self-regulate the release of insulin, based upon glycaemic levels. A nano-plug is prepared with cross-linked bovine serum albumin, glucose oxidase and catalase enzymes, pH-response hydrogel particles and multifunctional manganese dioxide nanoparticles. This plug is bound covalently to an insulin-reservoir made of silicone, which is PEGylated to ensure safety, biocompatibility and stability of insulin. The nano-plug detects glucose levels, and regulates release of insulin from the reservoir. This closed loop delivery device has been tested in type 1 murine models.

**Table-1: Classification of smart insulins.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONVENTIONAL</strong></td>
<td></td>
</tr>
<tr>
<td>Protein -binding ligand (lectin) -based</td>
<td></td>
</tr>
<tr>
<td>Membrane -based</td>
<td></td>
</tr>
<tr>
<td>Bulk hydrogel matrix based</td>
<td></td>
</tr>
<tr>
<td>Phenylboronic acid (PBA) - based</td>
<td></td>
</tr>
<tr>
<td><strong>NANO TECHNOLOGY</strong></td>
<td></td>
</tr>
<tr>
<td>Membrane -based</td>
<td></td>
</tr>
<tr>
<td>Microgel</td>
<td></td>
</tr>
<tr>
<td>Polymeric nanoparticle- cross-linked network.</td>
<td></td>
</tr>
</tbody>
</table>

**Microgel (Smart Sponge)**

Microgels (termed in lay media as sponges) have been developed to ensure regulated insulin release, in
response to ambient glycaemia. 10 The microgels, 256±18µm in size, are made by a one-step electrospray procedure, and consist of recombinant human insulin and enzyme nanocapsules in a pH-sensitive chitosan matrix. They include covalently encapsulated glucose specific enzymes. On exposure to hyperglycaemia, gluconic acid as formed, and the chitosan network pronated. Cleavage of gluconic acid allows insulin release, which is self-regulated. This system has been demonstrated to be effective in type 1 diabetes murine models.

Nano-Network
An injectable nano-network has been created for glucose-mediated insulin delivery. This network is composed of multiple components (Table-2).

**Table-2: Components of nanonetwork.**

<table>
<thead>
<tr>
<th>BASED SMART INSULIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid-degradable polymeric matrix of dextran (83% weight)</td>
</tr>
<tr>
<td>Surface coatings</td>
</tr>
<tr>
<td>Chitosan (positively charged)</td>
</tr>
<tr>
<td>Alginate (negatively charged)</td>
</tr>
<tr>
<td>Encapsulated enzymes (1.3% weight)</td>
</tr>
<tr>
<td>Glucose oxidase (GOx)</td>
</tr>
<tr>
<td>Catalase (CAT)</td>
</tr>
<tr>
<td>Recombinant insulin (17%, weight)</td>
</tr>
</tbody>
</table>

Double-emulsion based solvent evaporation/extraction method is used to create this dextran-based network, which contains insulin as well as the enzymes glucose oxidase and catalase along with insulin. 11

**Basic Principle of Smart Insulin**
Every smart insulin has to have two components: a glucose sensor, and an insulin delivery device. In the recently developed nano-network, exposure to hyperglycaemia leads to enzymatic catalysis of insulin nanoparticles, and allows release of insulin. The duration of action of these nanoparticles, and allow release of insulin. The duration of action of these nano-networks is 10 days in type 1 mice, and has been noted to last up to 14 days in some animal subjects.

**Summary**
The field of smart insulin seems to be a promising area for innovation. Patents have been drawn for glucose-responsive insulin formulations, including microgels, amphilic hydrogels, and thermo-sensitive polymers. 12-14 Patents are also filed for implantation insulin-producing devices which contain porcine endocrine cells contained in immuno-isolatory membranes. 16 All these research paths have potential to reach fructification.

There is criticism regarding the concept of smart insulin. It has been suggested that as insulin secretion follows a nonlinear pattern, any inorganic or non-living insulin secretory apparatus would not be able
to replicate the work of an organic, live islet of Langerhans. On the other hand, exactly the same limitation was thought to be true for computers and robots not so long ago. Recently an autonomous drug release system, based upon chemo-mechanical energy conversions, which works as an Organic Engine, without using external energy source, has been demonstrated to provide glycaemic control. This innovation has helped allay these fears.

Smart insulins are an exciting development in diabetes care. While it may take many years before they reach clinical use, recent advances in the area suggest that smart insulins will soon become a reality.

References