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REVIEW ON CLOSED LOOP DRUG DELIVERY SYSTEM

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ABSTRACT

Controlled drug delivery can improve the efficacy and safety of treatment by optimizing the timing and kinetics of release. Among these, closed-loop delivery strategies, also known as self-regulated drug delivery, have proven to be useful tools for maintaining homeostasis by modulating drug release according to the activity of biological signals that affect the body and pathological processes. A common example is glucose-releasing insulin, which can stimulate pancreatic beta cells to release the appropriate insulin at the appropriate time in response to plasma glucose. Similar self-regulatory mechanisms are also important in the treatment of other conditions such as thrombosis and bacterial infections. In this review, we examine recent developments in closed-loop antimicrobial responses, including glucose-sensitive, enzyme-activated, and other fire-fighting agents. We also discuss future opportunities and challenges in this area.

Keywords: closed-loop, drug delivery, bioresponsive, glucose-responsive, enzyme-responsive

1. INTRODUCTION

In organisms, homeostatic control plays an important role in regulating activity in a dynamic and changing environment, such as hormone secretion, ion balance, and immunity. Dysregulation of homeostasis underlies the pathogenesis of diseases such as diabetes and other autoimmune diseases [3, 4]. Over the past few decades, closed-loop drug delivery systems have been investigated as a promising alternative to traditional drug delivery for homeostatic control [5, 6, 7]. Unlike open-loop systems, which include immediate-release and sustained-release models, these smart drug delivery systems release adjustable doses over time, controlling the release of drugs according to biomarkers associated with pathological processes [8, 9]. A classic example is closed-loop insulin delivery systems, which release insulin only when necessary, such as high blood sugar levels [10, 11, 12]. They have anti-chemical and electronic properties that can cause drug release [13, 14, 15]. The integrated monitor/actuator architecture allows drug release at or above a given biosignal or threshold value, but is inhibited when the biosignal level is within the normal range [16, 17, 18].

2. GLUCOSE-RESPONSIVE CLOSED-LOOP INSULIN DELIVERY SYSTEMS

Correct and timely insulin administration is important for blood sugar control in patients with type 1 and type 2 diabetes (19,10). Open-label insulin use requires frequent blood sugar monitoring during or after meals and subcutaneous injections [20, 21, 22]. However, open insulin delivery currently has serious problems that prevent patients from achieving tight glycemic control and increase the risk of diabetes, including blindness, amputation, and renal failure [20,23]. A closed system that causes pancreatic β-cells to "secrete" insulin in response to blood glucose is thought to be a good strategy for the treatment of type 1 and late type 2 diabetes [4, 10].

2.1 Glucose oxidase (GOx)-based systems

2.1.1 pH

pH-sensitive polymer matrices containing glucose oxidase (GOx) were the first adhesive materials developed in the 1980s [24]. GOx, like glucose in blood, reacts with glucose in the presence of oxygen and converts it to gluconic acid, which causes the pH to decrease [25,26]. The pH-sensitive polymer matrix then swells in response to pH changes to stimulate insulin release. Peppas and colleagues have also used pH-sensitive hydrogels to synthesize glucose-releasing insulin, where the hydrogel expands or contracts in response to changes in pH to modulate central insulin secretion [27,28]. Building on this idea, several groups have developed glucose-like closed-loop insulin delivery systems using pH-sensitive materials in the past years [29,30,31,32,33]. We have developed an injectable polymer network consisting of GOx-loaded acid-degradable nanoparticles to enable insulin self-administration [34,35]. A pH-sensitive acetal material is used to replace dextran, and insulin and enzyme are encapsulated by the two-way emulsion. They form a gel-like nanonetwork by layering dextran nanoparticles separately with different types of polymers. The nanonetwork can sense blood glucose when injected into diabetic mice and then interact with the nanoparticles to secrete insulin when needed and effectively control blood glucose for up to ten days. Later, Tai et al. synthesized a glucose-sensitive diblock polymer containing a pH-sensitive amphiphilic polymer that self-assembled into nanoparticles with a polymer-structured structure for closed-loop insulin delivery [4].

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2.1.2 Hypoxia

Another way to use the decrease in pH as a trigger for drug release is to use oxygen as a signal during glucose oxidation to trigger insulin release [36]. 2-Nitroimidazole (NI), a hypoxia-sensitive group used in hypoxia imaging for cancer therapy, is conjugated to the side chain of hyaluronic acid (HA). The resulting amphiphilic polymers were able to self-assemble into nanosized vesicles to encapsulate insulin and GOx. As glucose increases, oxygen consumption during oxidation causes hypoxia, and the hydrophobic NI group is reduced to hydrophilic 2-aminoimidazole, which causes the nanoparticles to disintegrate and subsequently release insulin. To achieve easy administration, easy and painless [37,38,39].

2.1.3 H2O2

During the enzymatic oxidation of glucose, another byproduct, H2O2, is rapidly produced at high glucose concentrations. Therefore, H2O2-sensitive materials can also be used to recognize glucose-releasing insulin. Gu and colleagues developed block polymers composed of polyserine and polyethylene glycol modified with phenylborate (PBE) to deliver insulin [40]. The resulting copolymers are amphiphilic and self-assemble into polymeric nanoparticles to encapsulate insulin and GOx. Upon exposure to high blood glucose, H2O2 is rapidly formed and readily interacts with the block polymer, disrupting the suspended PBE, increasing the water solubility of the polymer, and promoting the gradual dissociation of the nanoparticles for insulin release. They also implanted H2O2-sensitive nanoparticles into painless microneedle patches in in vivo studies, showing that blood glucose remained normal during the first 5 h of application in type 1 diabetic mice [41].

2.2 Glucose binding proteins (GBPs)-based systems

In the past decade, various insulin delivery strategies based on selective binding of GBP and glucose have been developed [41, 11, 10]. The lectin, concanavalin A (Con A), obtained from the concana bean, is frequently used as a glucose-sensing moiety [42].

Con A has four binding sites with opposite affinity for D-glucose, D-mannose, and polysaccharides [43,44]. In the 1970s, Brownlee and Cerami first used Con A to produce glucose-regulating insulin, taking glycosylated insulin derivatives and conjugating them with Con A [43]. Insulin derivatives are released by competing for free glucose in the presence of increasing glucose. Kim and colleagues also developed gluconic acid-modified insulin to be coupled to concanavalin A to achieve self-releasing insulin [45,46].

In addition, reversible binding of Con A and polysaccharides such as dextran and chitosan allows glucose formation in hydrogel materials. For example, Nie and colleagues developed glucose-stimulated insulin hydrogels that can swell and release insulin by hydrolysis when glucose levels increase. [47,48].

2.3 Phenylboronic acid (PBA)-based systems

PBA is a synthetic compound that can combine with diols to create a cyclic boronate ester with five or six members [49]. PBA-based devices have been extensively used for closed-loop insulin delivery, glucose sensors, and diabetes diagnosis since Lorand and Edwards discovered the reversible binding between PBA and sugar in 1959 [50,51,52].

3. ENZYME-RESPONSIVE CLOSED-LOOP DELIVERY SYSTEMS

Numerous biological and metabolic processes depend heavily on enzymes, and the development of numerous disorders is linked to the dysregulation of enzyme expression [53,54,55]. As a result, certain enzymes serve as both promising triggers for particular medication delivery and crucial diagnostic signals[56].

3.1 Thrombin

For instance, thrombin is the primary enzyme in the blood coagulation cascade and is in charge of changing soluble fibrinogen into insoluble fibrin [57]. Vascular occlusions and serious cardiovascular disorders can result from abnormally high blood thrombin levels [58,59].

To prevent such coagulation activation, heparin, a common anticoagulant, is administered in exact dosages [60]. Maitz and colleagues developed a direct control loop device to provide heparin in dosages adjusted by the ambient thrombin levels in order to more accurately dose heparin levels and avoid related adverse effects[58].

3.2 Lipase

When bacterial and fungal infections occur, secreted lipases play a crucial role in persistence and pathogenicity [60]. Therefore, in order to specifically suppress the development of bacteria and fungi, a lipase-activated drug delivery method has been investigated. Wang and colleagues, for instance, reported a lipase-sensitive polymeric triple-layered nanogel for drug delivery activated by bacteria[61].

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4. OTHERS BIOSIGNALS-CONTROLLED CLOSED-LOOP SYSTEMS

4.1 CO2

Closed-loop drug delivery systems also hold great promise for controlled-release reactions to opioid overdose. Morphine is an opioid analgesic used to relieve acute and chronic pain [62–64]. However, morphine overdose can cause decreased respiration and blood pressure, decreased blood oxygen levels, increased carbon dioxide levels, and death from acidosis. Proper administration of analgesics can eliminate the risk of morphine overdose. Thus, Heller and colleagues developed a morphine-triggered antidote device consisting of a drug-loaded, enzyme-coated, erodible polymer core and cellulose dialysis tubing that can deliver morphine-triggered antidote to the infant as lipase, which is covalently bound to morphine antibodies and complexed with them, is inactivated [66]. Free morphine can eliminate the lipase-morphine complex in the reaction and allow rapid degradation of the polymer core to release the drug. Sataf et al. Another self-regulating immune system developed using carbon dioxide as a danger signal [67]

4.2 Urea

Based on urease's enzymatic activity, which hydrolyzes urea into NH4HCO3 and NH4OH, urea-responsive drug delivery has also been investigated [68]. Heller and Trescony created a urea-responsive delivery system based on a pH-sensitive bioerodible polymer because this enzymatic process raises pH [69]. A partly esterified copolymer of methylvinylether and maleic anhydride was combined with a model medication, hydrocortisone, to create disks that were then covered in urease-immobilized hydrogel. The pH rise was able to quicken the drug release and polymer disintegration in the presence of exogenous urea. Similarly, for urea-responsive closed-loop administration, Ishihara et al. created a pH-sensitive membrane in place of the erodible polymer. [70,71].

4.3 Ions

Because bodily fluids like blood, gastrointestinal fluid, sweat, and tears include a wide variety of cations and anions, ion-responsive delivery systems are able to detect the quantities of these ions in bodily fluids and adjust the rate of medication release for the best possible treatment. For example, Huang et al. reported a Na+-sensitive alginate gel loaded with nano-silver as a non-specific antimicrobial agent for wound dressing applications. Na+ ions are frequently found in wound exudates[72].

5. CONCLUSIONS AND FUTURE DIRECTIONS

Over the past few years, many forward-thinking concepts have emerged that provide new control strategies for the creation of closed drug delivery systems. For such systems, many bioresponsive materials are being used to create functional models of the desired materials.

Therapeutics are designed to control the release of drug carriers through structural changes such as contraction, swelling, and dissociation, or through non-uniform pathways. Table 1 describes the closed-loop drug delivery systems recently reported in this review. Smart devices have now been found to improve therapy and reduce unwanted drug delivery, showing great potential in areas such as diabetes management, diabetes management self-esteem, and antibiotic therapy in both research and clinical settings. Despite progress, the translation of effective treatment and safe closed-loop delivery faces challenges in many areas. For example, to achieve good delivery, the product is not necessarily related to the information and the design must be carefully tailored. It is also important to ensure consistency in the evaluation of tools in clinical trials. Second, a better understanding of the role of biomarkers in diseases is needed to develop closed-loop systems. It is important to separate the signal of interest from its analogs to improve the specificity of delivery. In addition, long-term prevention and treatment of closed loop should have sufficient and effective biocompatibility. Comprehensive evaluation of data and elimination of harmful chemicals should be considered. In addition to these challenges, the identification and use of new agents/actuators are also important for the development of new medical devices, especially for metabolic diseases..

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