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Review Article

Recent developments in blood glucose sensors

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ABSTRACT

Diabetes has recently become a leading cause of death worldwide. To date, although there is no means to cure or prevent diabetes, appropriate medication and blood sugar monitoring can enhance treatment efficiency, alleviate the symptoms, and diminish the complications of the condition. This review article deals with current growth areas in the market for blood glucose sensors and possible future alternatives, which are generally considered to be the point sample test and the continuous glucose monitor (CGM). Most glucose sensors are enzyme-based, whereas others are enzyme-free. The former class is sensitive and some products are extensively employed for daily self-sensing and in hospital environments as reliable diagnostic tools. The latter class, particularly the boronic acid fluorescent sensor, is facile and extremely promising. Practicality demands that all types of sensors offer accuracy, specificity, and real-time detection.

1. Introduction

Since Emil Fischer established the monumental theory of supramolecular chemistry on interactions between substrate molecules and specific enzymes, molecule recognition is of particular interest to numerous scientists [1]. Molecular recognition based on the lock-and-key principal occurs in biological systems such as enzyme–substrate interactions, antigen evoking antibody [2–5], and sugar binding to lectin [6–9]. Following development of the first two-dimensional structure of crown ether for a specific metal ion by Pedersen, Cram, and Lehn [10], the possibility of synthetic receptors that mimic important biological activities was demonstrated. Particularly, saccharide recognition attracts the attention of biochemists and medicinal chemists not only because saccharides are involved in cell–cell interactions within biological organisms but also because saccharide sensing offers promise for clinical diagnostic applications such as blood sugar level, pathogens, and cancer [11–18].

2. Saccharides and their importance

Carbohydrates, the most abundant organic form of material on the earth, which form biological building blocks and dietary components, are classified as single sugars (monosaccharides) and their polymers, namely oligosaccharides and polysaccharides [19–21].

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Monosaccharides are generally the simplest and most basic of carbohydrates, serving both as energy fuels and fundamental constituents of living organisms. For example, five-carbon sugars exist in information carriers, such as deoxyribose in DNA and ribose in RNA; moreover, the best-known six-carbon sugars include D-glucose, also known as either grape sugar or blood sugar; D-fructose, fruit sugar; and D-galactose, which forms milk sugar when combined with glucose. The D series of sugars are thus designated based on the observation that most natural monosaccharides have the same configuration at C-5 as D-glyceraldehyde. In aqueous solution, the isomeric structures of glucose molecules display equilibrium. In neutral solution, glucose exhibits the linear open-chained form in <0.1% of molecules. Most of these molecules exist as a more stable cyclic hemiacetal with a six-membered pyran ring and thus are termed the pyranose (Fig. 1).

In humans, D-glucose is vital for its role in metabolic homeostasis; it acts as an energy source in living systems and maintains human bodily functioning when consumed or through the formation of other essential saccharides via biosynthesis. When taken up by human cells, glucose can be either broken down (glycolysis) to yield energy, converted into other metabolites in the form of metabolic intermediates, or polymerized to form cellulose and starch through biosynthesis to function properly. In the human body, besides existing in free form, glucose can covalently link to lipids (glycolipids) and proteins (glycoproteins) and other biological molecules as glycoconjugates, which are crucial building components of cell membranes and are mainly involved in the mechanism of intercellular recognition [22].

Monosaccharides can also join other sugars via glycosidic bonds through the sequential reaction of their anomeric hydroxyl groups with the hydroxyl groups of other sugars, together with the elimination of water, resulting in a yield of oligosaccharides or polysaccharides. The simplest and most biologically important oligosaccharides are disaccharides. Three naturally abundant disaccharides are maltose, lactose, and sucrose. The glycosidic linkages of these three disaccharides are formed stereospecifically by enzymes; therefore, only one of the possible configurations (α or β) occurs and, like all glycosides, its mutarotation is not permitted. Maltose, which occurs mainly in malt, comprises two D-glucose units joined with an $\alpha(1\rightarrow4)$ bond via a condensation reaction. Lactose, the most important sugar in mammalian milk, is the combination of D-galactose and D-glucose. Sucrose, also named table sugar, consists of D-glucose and D-fructose. Oligosaccharides also form glycoconjugates with proteins and lipids, some of which are important in cell biology. Additionally, taking advantage of their biological effects, complex oligosaccharides and their analogs are widely

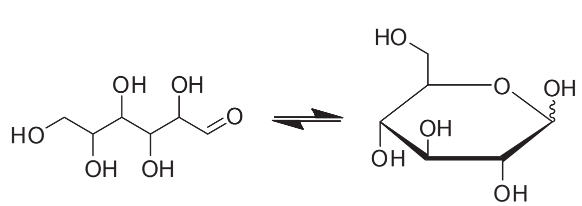

Fig. 1 – Linear and cyclic form of D-glucose.

applied in pharmaceuticals. For example, the first oligosaccharide analog used as a chemotherapeutic agent was streptomycin, a bactericidal aminoglycoside antibiotic isolated in 1943, and also the first cure for tuberculosis. Acarbose, an antidiabetic drug used to treat type II diabetic mellitus by inhibiting α-glucosidase, localized in the brush border of intestinal epithelium, is also an oligosaccharide derivative comprising two glucose moieties with a rare sugar unit. Cyclic oligosaccharides such as cyclodextrins, obtainable by partial hydrolysis of starch, which bear a hydrophilic exterior and hydrophobic interior, can form host–guest complexes and be applied in drug delivery systems (Fig. 2) [21]. Cyclodextrins also have numerous applications in foods, pharmaceuticals, chemicals, and agriculture.

Polysaccharides, macromolecules comprising numerous monosaccharide moieties, are ubiquitous in nature. They are frequently classified into three classes according to function: structural polysaccharides, water-binding polysaccharides, and reserve polysaccharides. Polysaccharides are important biological polymers and possess great structural diversity.

3. Glucose-related disease: diabetes

Various saccharides-related diseases are common in clinical practice, including disorders of carbohydrate metabolism, such as lactose intolerance, Andersen's disease, Pompe disease (acid maltase deficiency) [23,24], obesity, hypoglycemia, hyperactivity (mostly in children), and most important of all, diabetes [25–27].

Diabetes is a chronic disease that has devastating human, social, and economic consequences. According to the World Health Organization (WHO) and the International Diabetes Federation, its worldwide prevalence is projected to double over the next couple of decades, from 347 million people in 2005 to 700 million people in 2030. Notably, >80% of diabetic patients live in low- and middle-income countries [25,28].

Diabetes can be divided into three main types. Type I diabetes is insulin-dependent; it was previously called insulin-dependent diabetes mellitus or juvenile diabetes. It is caused by deficient insulin production within the body and typically manifests among the youth. Daily replacement of insulin becomes indispensable for those with the condition. Type II diabetes is noninsulin-dependent and is caused by insulin resistance, a condition in which the target organs develop a failure to properly respond to insulin. Type II diabetes is termed adult-onset diabetes and makes up >95% of all cases. Gestational diabetes occurs when pregnant women, usually without a previous history of diabetes, develop a high blood glucose level. Women with gestational diabetes typically have a high risk of eventually developing type II diabetes.

Although diabetes is not actually caused by saccharides, it is one of the most notorious saccharide-related diseases. This is because body cells cannot digest glucose from blood themselves. To maintain blood sugar concentration following ingesting carbohydrate, the body requires insulin, produced and released from the B- (or β-) cells of the pancreas, to transport glucose into cells for subsequent metabolism. The result of inefficient insulin production or secretion is an excessive rise in blood glucose, even spilling into the urine.