Sensors and Actuators B 161 (2012) 45–79

Contents lists available at SciVerse ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Review

Arylboronic acids: A diabetic eye on glucose sensing

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ARTICLE INFO

Article history:
Received 13 September 2011
Received in revised form
29 November 2011
Accepted 11 December 2011
Available online 17 December 2011

Keywords:
Arylboronic acids
Diabetes mellitus
Semi-invasive
Non-invasive
Fluorometry
Colorimetry
Electrochemistry
Surface immobilization
Imprinted polymers

ABSTRACT

Tight control of blood glucose is the most important goal in the treatment of *diabetes mellitus*. This limits the long term consequences, which include damage to the heart, eyes, kidneys, nerves and other organs, among others, caused by malign glycation of vital protein structures. Proper clinical glucose control is difficult, since many factors influence the glucose concentration. Handy blood glucose monitors have been available for over a decade and have improved the general control and prognosis of the patients. Such meters however require invasive events and are thus inconvenient to the patient. Approaches towards semi-invasive and non-invasive methods have been made, but despite a lot of effort, no practical solutions, which provide proper comfort, have been reported so far. Arylboronic acids potentially have applications as optical or electrochemical reporters that can replace the commonly applied semi-invasive and non-invasive techniques relying on glucose-binding proteins, such as concanavalin A or enzymes such as glucose oxidase, glucose dehydrogenase, and hexokinases/glucokinases. Arylboronic acids are capable of providing immediate information of glucose concentrations, due to the fast and reversible formation of esters with 1,2-*cis*-diols or 1,3-diols of the glucose molecule. Arylboronic acids potentially offer non-invasive continuous blood glucose monitoring, in some cases without the need for reference measurements. The information can be provided by attachment of the boronic acid moiety to a proper reporting unit, which undergoes a significant change in fluorescence emission/lifetime, a significant colorshift or a significant shift in the redox potential.

This review will focus on the important properties of boronic acids which eventually will make them suitable as key elements in future non-invasive continuous glucose sensors. We will further emphasize the developments made in boronic acid based polymers, imprinted polymers, and surface immobilized boronic acids as such materials may enhance key properties, such as selectivity, sensitivity and binding strength of arylboronic acids significantly.

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0925-4005/$ – see front matter.
doi:10.1016/j.snb.2011.12.024

1. Introduction

Tight control of blood glucose is the most important goal in the treatment of diabetes. This will limit the long term consequences of the chronic disease including damage to the heart, eyes, kidneys, nerves and other organs. This damage is among others caused by high glucose concentrations, i.e. hyperglycemia. This state results in malign glycation of proteins e.g. by Schiff-base condensation between a sugar aldehyde and a free amino group. The consequences of this process are inactivation of enzymes and alterations of vital membrane structure. This reduces the elasticity and renders the membranes more fragile [1–3].

These complications can be greatly reduced through stringent personal control of blood glucose, employing frequent blood glucose monitoring and corresponding insulin administration. This results in proper glycemic control is however a difficult task, because a plethora of factors influence the glucose concentration, such as timing of meals, type and dosing of insulin, exercise, infections, etc. The healthy concentration interval of D-glucose is narrow, ideally 4–6 mM. Blood glucose monitors have been available for over a decade and have helped in administering insulin, and further improved the prognosis for diabetes patients [4,5]. Continuous blood glucose monitoring provides a much better surveillance as compared to an intermittent monitoring, despite the fact that the latter displays a higher accuracy [2,6]. A key property of a continuous monitor is the predictability of future glucose concentrations, due to the constant surveillance. This cannot be offered by an intermittent monitor. This control will minimize unwanted fluctuations in blood glucose. A further advantage of the continuous monitor is the ease of performing proper glycemic control. The intermittant monitor requires more operating effort in comparison.

The commonly employed intermittent glucose sensing devices are based on electrochemistry, i.e. oxidation of glucose to gluconolactone by the glucose-oxidase enzyme (GOx) [7,8]. This sensing method is invasive and thus inconvenient, due to the requirement of a blood sample.

Semi-invasive glucose monitoring provides significantly less discomfort and pain in comparison to their invasive counterparts [9,10]. These systems are based on very sensitive techniques, which include fluorescence intensity and lifetime. The lectin concanavalin A (ConA) [11], enzymes such as glucose oxidase [12], glucose dehydrogenase [13], hexokinase/glukokinase [14], bacterial glucose-binding proteins [15] and boronic acid derivatives [16] are usually employed.

Some challenges to overcome for semi-invasive monitors are the demands for miniaturization, long-term stability of the enzyme and transducer, oxygen deprivation, in vivo calibration, powering, short stability, baseline shift, safety and convenience [17–21]. Implementation requires a very tiny sensor size and proper shape to minimize the discomfort [17]. Inflammatory response to the implementable sensor in the subcutaneous tissue leads to formation of fibrous capsules around the chemical sensors.

With these things in mind, the elusive goal is the development of a non-invasive glucose monitoring device. This is expected to eliminate the challenges, pain and discomfort associated with the implantable devices. Non-invasive glucose monitoring has been directed towards measurements of glucose in tears, saliva or sweat. A major disadvantage of this approach is its intermittent nature, because all of these fluids need to be collected before performing a measurement [22].

Cygnus Inc. developed a watch-like glucose monitor, using iontophoretic collection of glucose across the skin as the biosensor function [23]. The GlucoWatch device, previously available from Animas Technologies Inc., contains both the extraction and sensing functions along with operating and data-storage circuitry. Monitoring can be performed for a 12 h period with 3 readouts per hour [17]. Readouts are performed by electro-osmotical extraction of glucose, with a clinically acceptable level of accuracy. Disadvantages of this device include long warm up times, calibration against glucose from a finger stick and skin rash from the device, and it is only approved for trend setting in collaboration with a clinician; not for home care insulin administration.

The use of tear glucose as an indicator for blood glucose levels is widely discussed. A poor correlation, between tear- and blood glucose levels, was found in a study reported by LeBlanc et al. [24]. However, recent investigations by Baca and co-workers found a correlation [25,26]. The authors suggested that the discrepancy is caused by a bias in the results.

Despite a lot of effort in the area of developing semi-invasive and non-invasive methods, no practical solutions that provide comfort have been reported so far.

Several reviews have been published about glucose sensing [27–31], but this review will focus purely on arylboronic acids and their application as glucose sensing devices.

2. Arylboronic acids for the monitoring of blood glucose

The applications of arylboronic acids as carbohydrate sensors are broad, because they are small and flexible molecules. They can easily be incorporated as recognition motifs into larger structures, e.g. proteins, without changing the physical properties dramatically [32]. Another great advantage of arylboronic acids is their fast and reversible formation of cyclic esters with *cis*-1,2-diols or 1,3-diol compounds in aqueous media [16].

In 1992 Yoon and Czarnik pioneered a new era in carbohydrate recognition [33], by applying a principle first introduced by Böeseken [34,35] and later modified by Kuivila and others [36–40]. Yoon and Czarnik introduced the use of aromatic boronic acids for carbohydrate sensing by combining the fluorescence properties of an anthracene core with the binding properties of a boronic acid. As shown by the early work [34–40], arylboronic acids are capable of forming cyclic esters with compounds containing diol moieties. This specific feature led to the still growing field of arylboronic acid based carbohydrate sensing [32,41–45].

Development of a proper arylboronic acid, for use in semi-invasive or minimally invasive spectroscopic sensors, would be a great step towards improving the glycemic control of diabetic patients. Development of a spectroscopic probe giving a significant response upon a recognition event is desirable. The spectroscopic monitoring can rely on colorimetry, i.e. a significant color change upon glucose binding, or a significant change in the band of emission or intensity for fluorescent probes. Fluorescence-lifetime based sensing of D-glucose may solve many calibration problems in carbohydrate sensing. With the right choice of wavelengths, i.e. the near-infrared area with $\lambda > 600$ nm [46], such measurements can be