Mini Review

A mini review on the use of biosensors for indirectly assisting the diagnosis of fibromyalgia

Abstract

Fibromyalgia (FM) is a syndrome known mainly for causing muscular and skeletal pain, whose etiology still remains unknown. Besides intense pain, FM patients can also present a clinical picture of fatigue, insomnia, headaches and intestinal changes. One of the most important challenges related to the disease is the difficult diagnosis, which can be confusing because it presents symptoms common in many other pathologies (like anxiety and depression). Some characteristics that can contribute to a better diagnosis are the differences in the level of certain biological molecules, such as some hormones and markers. The conversion of the information referring to the levels of these biological compounds into a measurable analytical signal is the focus of some biosensors recently reported in the literature. These devices are expected to collaborate in increasing the reliability of the indirect FM diagnostics. In this sense, this mini review presents an overview on the recent trends on the fabrication of some biosensors based on different transduction mechanisms and bioreceptors to detect analytes of interest for the indirect diagnosis of FM.

Keywords: fibromyalgia, biosensor, diagnosis

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Introduction

Fibromyalgia (FM) is a chronic disease with a complex multifactorial etiopathogenesis not yet fully known. One of the most noticeable symptoms in most cases is chronic and generalized pain in the muscles and bones,[1,2] the absence of inflammation in the joints and muscles and the activation with pressure on the local site. More typical in females (approximately 80% of the reported cases), the disease is present in 2-4% of the world population,[3] especially when factors that contribute to stress are also present, such as: anxiety, insomnia, chronic headaches, neurological problems, intestinal problems and especially depression.[4] Other factors that favor increased pain in FM patients are mainly obesity, poor diet and physical inactivity.[5]The treatments of FM vary from the use of medications and psychological/psychiatric monitoring to the increase in the amount of physical activities performed by the patient, which contributes to general well-being, physical capacity and sensitization to palpation.[6] One cause of the constant misinterpretation in the FM diagnosis is the presence of symptoms that are common to other several injuries. Studies indicated high concentrations of thyroid-associated hormone (TSH) in patients previously diagnosed with FM, in addition to other changes such as lower secretion of triiodothyronine (T3) and tetraiodothyronine (T4), which can be defined as difficulties in thyroid production or use of what it produces. The association is also made because symptoms such as muscle pain, non-restorative sleep, fatigue, decreased physical capacity and cold intolerance are symptoms of some other diseases[7] in addition to the higher frequency of hypothyroidism in fibromyalgia.[8] The disease, which is a chronic multisystemic inflammatory process,[9] can be caused due to the generation of antibodies by the imbalance of the immune system. Antibodies bind to their antigens to form immune complexes that activate the complement system, initiating chemotaxis (changes in cell orientation thanks to chemical stimuli) and tissue inflammation.[10] There is, then, a difficulty in diagnosing an individual with FM as there are many clinical variables linked to the disease. According to Ribeiro,[11] the causes of FM are uncertain and the results contain a considerable discrepancy, which leads one to believe that it is caused by combined factors.

In addition, the form of FM assessment has changed significantly in recent years, which can be confusing for the conclusion of the final diagnosis. One of the difficulties would be in the process of measuring the individual biological signals (such as certain hormones and/or antibodies levels, for example), which would contribute to the identification not only of FM, but also of several other disorders. Among the conventional techniques employed to measure biological molecules (enzymes, DNA, antigens, antibodies, whole cells and organelles), the use of biosensors has gained special visibility in the past years.[12]The use of biosensors has reached great importance with regard to discoveries in the field of food safety, clinical analysis and biochemistry in general.[12] Biosensors are practical devices of high cost-benefit and considerable precision, which use a selective activity through a biological recognition layer combined with a transducer substrate.[13] The transducer converts the captured signal into a measurable signal proportional to the concentration of the target molecule.[14]Given the addressed context, the present study aimed to review the literature on the use of biosensors for assisting the diagnosis of FM through the detection of molecules indirectly associated with the disease.

General aspects of FM

Since the first researches, it was found that FM affects, in most cases, women mainly with some of the following characteristics: age group around 35 to 60 years old, greater tendency to depression and higher levels of low morning cortisol.[15,16] However, it is worth noting that men and women out this age group are also diagnosed with the disease, causing researchers to make other more relevant associations, such as depression and anxiety, which are common ailments for people with FM. Many patients with FM can be misdiagnosed with depression, high levels of stress, some type of anxiety disorder and/or other rheumatological problems. Because FM does not have physical characteristics that can be related to the disease, patients can be treated within a certain level of disbelief.[3]

Treatment

Fibromyalgia treatments are diverse, ranging from medications

to physical aerobic exercises, therapy and various mental relaxation processes. Some drugs that have been used in the treatment are:

I. Tricyclics such as cyclobenzaprine (which showed little improvement in sleep) and amitriptyline (with a chance of reducing pain by up to 30%);

II. Gabapentinoids such as pregabalin (which showed considerable pain reduction)[17] and gabapentino (without enough evidence to support that its use reduces FM pain);[18]

III. Norepinephrine and serotonin reuptake inhibitors (small improvement in patients' sleep and disability) and moderate effect on pain without effect on the feeling of fatigue;[19]

Cannabis use is also presented in the literature, showing considerable results.[20]A series of non-medicated treatments for FM patients were also observed in the literature. In this context, some physical exercises showed beneficial results in treating the disease, such as hydrokinesiotherapy, resistive training (RT), which is any type of exercise performed against resistance and daily physical activities, massage techniques and meditation.[21–23]

Challenges in the current diagnosis

The American College of Rheumatology (ACR)[24] defined some diagnostic criteria in 1990 to determine the presence of FM, such as the occurrence of pain on the two sides of the body, in regions above and below the waist for a minimum of 3 months and the presence of at least 11 out of 18 possible tender points. Twenty years later, though,[25]ACR associated FM diagnosis to the observation of sleep, fatigue, cognitive disorders and some somatic symptoms. Referring to the fragility of these indications, Cohen[26] pointed out that the mentioned tender points are not exclusive to FM patients and they can be related to psychological distress and female sex with no relation to age. Moreover, the author reported that the 2010 ACR criteria does not comprise information concerning the severity of the main symptoms (sleep, fatigue and cognitive disorder).A characteristic that differentiates FM from other syndromes can be the alteration on the level of certain hormones in the body, such as the profile of adrenocorticotropic hormone (ACTH) with cortisol that becomes elevated at night in fibromyalgia patients. There is evidence of differences in the regulation of the hypothalamic axis of the pituitary gland between fibromyalgia and other central sensitization disorders. In their findings, Qu et al.[27] demonstrated that the levels of corticotrophin-releasing hormone (CRH), cortisol, gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone TRH, interleukin 1 (IL 1β) and factors of tumor necrosis alpha (TNF-α), which is an important marker of inflammatory processes in the human body, were significantly higher in FM patients, while T3 and T4 were significantly lower in these patients. Thus, these data can be useful tools for the identification of FM in patients with suspected disease.

Biosensors as a tool of diagnosis

Given the plural possibilities involving analytes of interest, units of biological recognition, substrate materials and transduction techniques, the technology of biosensors has conquered an important position in the science of diagnosis. The application of biosensing platforms in the detection of molecules of clinical interest are required because of the intrinsic characteristics they possess manly with respect to their sensitivity and selectivity as well as due to the necessity of health monitoring in the medicine field. Baglioet al.[28] pointed out that the relevance of monitoring of critical patients' health

in both pre-intensive and intensive care. The authors mention that the former can provide useful information to the early and rapid treatment and the latter requires constant control (24h/day observation) in order to control vital signals.Considering the specificities of the FM, which heavily rely on the challenging current diagnosis and the severity of its clinical nature, the use of biosensors to indirectly detect FM-related illness seems to be a promising complementary tool for the FM diagnosis.

Definition and technological aspects

Biosensor is a device that, by binding a target analyte to its sensitive domain, converts the physicochemical signal generated during the biorecognition into a quantitative or semi quantitative output signal.[29] The element responsible for binding the target molecule, the bioreceptor, is generally the first choice in the development of a biosensor because its characteristics strongly determines the resultant sensitivity and selectivity of the device. In this group, the main elements used for biorecognition are enzymes, antibodies, nucleic acids and aptamers.[30] In order to attach the bioreceptor to the transducing surface of the biosensor, one must take in account the organic nature of these molecules as well as the features and properties of the substrate. The transducer is the element responsible for supporting the bioreceptor and properly convert the input signal from the bioreaction to the output measurable signal. This element presents a crucial role in the biosensor because it is intimately related to the efficiency in amplifying the measured signal, achieving the desired sensitivity and linearity. Depending on the transduction mechanism, a biosensor can be classified mainly as optical, electrochemical, piezoelectric and thermal. The advantages and drawbacks of each of each of the transduction techniques have been deeply studied in the literature to achieve the high performances in the field of clinical diagnosis.

Indirect diagnosis of FM

FM can cause various types of disorders and can be associated with other disease(s), which consequently tends to interfere negatively in the human's health. Thus, the detection of those indirect disorders can be used to indirectly assist in the diagnosis of FM.Within the studied literature, the use of several types of biosensors was reported with regard to the detection of some molecules that may be associated with FM. An example is a non-faradic biosensor containing MoS_2 nanoparticles integrated with a flexible nanoporous electrode system for detection of cortisol within the physiological range of 8.16 to 141.7ng/mL.[31] Cortisol is a marker of stress released by the hypothalamus-pituitary-adrenal axis (HPA), whose deregulation in blood is commonly noted in FM patients.[32]A paper-based electric biosensor used to quantify salivary cortisol was proposed by Khan et al.[33]and presented a high specificity and sensitivity, with a limit of detection (LOD) equal to 3pg/mL in an analytical range from 3pg/mL to 10μg/mL. Other types of biosensors towards cortisol quantification were found in the literature employing different transducing matrixes.[34–37]According to Quet al.[27] the changes in the level of certain other hormones in humans can also be an indicative of the FM manifestation. In their findings, Li, Larin and Kerman[38] demonstrated the development of a miniaturized immunosensor for the highly sensitive detection of Adrenocorticotropic hormone (ACTH) through Electrochemical Impedance Spectroscopy technique. Employing silkscreen disposable gold electrodes, the study demonstrated that the proposed biosensor possesses high potential to detect ACTH at low concentrations (LOD=100fg/mL) in a required sample volume of only 5μL. Chou et al.[39]fabricated an ultrasensitive electrochemiluminescence

immunosensor to detect 3,3',5-triiodothyronine (T3). The quantitative measurement of T3 could be reached in a range of 0.1pg/mL to 0.8 ng/mL in the presence of serum.

The research of Pohanka[40] demonstrated the detection of tumor necrosis factor alpha (TNFα) through a piezoelectric immunosensor as a functional alternative when compared to the conventional Enzyme-Linked Immuno-Sorbent Assay (ELISA). This marker is an important cytokine in the human inflammatory process and its correlation to microglia in the central nervous system can be correlated to the FM pathology. Besides not suffering significant interference from interleukin 6 nor human serum albumin even at higher concentrations than the maximum physiological concentration they are expected to be found, the fabricated immunosensor was capable to detect TNFα at 1.62pg/mL (sufficient LOD). The piezoelectric device was proved to be enough sensitive and the obtained results were in good agreement with those obtained by ELISA standard test, corroborating its considerable reliability and practicality. Furthermore, the author mentioned that the immunosensor possesses as extra advantages over ELISA its simplicity and the possibility of use in field conditions as well as in daily homecare. As another disturb present in FM patients, anxiety can be caused by many different internal/external factors. According to Pinto et al.[41] factors that lead an individual to high and continuous stress can be directly related to a picture of anxiety and/or depression. The organic response of the individual's organism when subjected to stress can be described in phases, where the individual first receives energy thanks to the production of adrenaline. In the last phase, the phenomenon of exhaustion occurs when stressful factors remain constant and intense, which can lead the individual to develop some psychological disorders. In light of this context, Molinnus et al.[42] used an amperometric biosensor using a substrate recycling principle for the detection of low concentrations of adrenaline in phosphate buffer (pH 6.5) and Ringer's solution (pH 7.4). The authors modified a self-polarized commercial galvanic oxygen sensor with a membrane containing the bienzime system of laccase and GDH. The results demonstrate the ability of the biosensor to rapidly and qualitatively determine the presence of adrenaline (at approximately 1nM) using the Boolean logic-gate principle. Another report of Molinnus et al.[43] in the literature also described an amperometric enzymatic biosensor to detect adrenaline. This one was prepared by means of an oxygen electrode with laccase operating between 3.5 and 8.0 pH range. The sensor measured oxygen consumption due to oxidation of adrenaline by the enzyme. The results showed the maximum sensitivity to adrenaline (detected up to 3 μM).

In both anxiety and depression cases, there may be changes in hormones such as endorphins and serotonin. Using a simple and promising technique, Marquez et al.[44] presented a non-enzymatic biosensor combining the use of nanotechnology with the measurement of phosphorescence emission for the determination of serotonin in human serum. The authors point out that, despite there are several assays employed in the detection of serotonin (mainly enzyme immunoassays and ELISA), these traditional methods are very sensible to temperature due to the instability of enzymes, they require multiple steps to be performed and, consequently, are time-consuming and expensive. The results were mainly highlighted for solving two major issues according to the authors: the capability to detect the target in the complex human serum (which is composed by several interfering species, such as proteins, hormones and vitamins) and high sensitivity compatible to the real application, once this analyte is normally found in serum at concentrations ranging from 40 to 450ng/mL.

Conclusion

Although there are some drugs available on the market to relieve pain and other symptoms of FM, they can cause some side effects mainly depending on the dosage and the level of impact of FM on the patient. Aerobic exercises show considerable improvements in the clinical picture as it increases the quality of life by means of the better sleep quality as well as increasing the levels of dopamine and other hormones that are beneficial to health. One of the greatest difficulties that still exist concerning FM is its diagnosis, which is extremely important for all the actions taken after the confirmation or not of the disease. There is still some difficulty in identifying such pathology, especially when the diagnosis is made through the elimination of the possibility of other supposed diseases. Thus, studies of indirectly related molecules become valid to assist the FM diagnosis. The detection of the levels of certain substances in the patient body can collaborate for more reliable analysis on the possible manifestation of FM. In this way, biosensors represent a promising valuable tool by measuring levels of various hormones and other biological molecules that can indicate abnormalities caused in the body of FM patients. In this research, we reviewed the literature on the application of several biosensors containing different bioreceptors to detect molecules of medical interest that can be related to FM. The most common transduction mechanisms were the optical and electrochemical ones, combined to which the enzymes and antibodies were widely employed to achieve high performances and to overcome the drawbacks of traditional techniques (complexity, high cost, longtime performance, interference from other molecules than the target analyte, impossibility of use in field applications, etc). Recent researches on the biosensing of hormones and biomarkers have demonstrated low LODs and high selectivity even in human serum, a complex biological solution which possesses many interfering species. Accordingly, the recent studies on the field of biosensors for detection of molecules indirectly related to FM have represented an important step towards a more accurate and reliable diagnosis of this illness.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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