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Mini Review

Electrochemical Biosensors with Butyrylcholinesterase. Period 2016-2022. A review

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Butyrylcholinesterase (BChE) biosensors are analytical devices with BChE as a biorecognition element for specific interaction with an analyte. They serve to detect various compounds from which group organophosphate and carbamate neurotoxins are probably the most important. The BChE biosensors can be used in a way similar to that of the more widespread acetylcholinesterase (AChE) biosensors. Compared with the AChE, the BChE biosensors are less sensitive to the inhibition of some natural toxins and can work with many enzymatic substrates. In the last few years, new applications of BChE have been described, and advanced materials and analytical methods have been implemented into practice. This review focuses on the comparison of BChE biosensors with the other types of analytical devices applicable for neurotoxic compounds assay, an explanation of the assay principles, and an introduction of relevant papers from recent years.

Keywords: acetylcholinesterase; amperometry; assay; enzyme; inhibitor; neurotoxin; nerve agent; pesticide; potentiometry; sensor

1. INTRODUCTION

Neurotoxic compounds inhibiting cholinesterases are a wide group of harmful substances that include pesticides such as carbofuran, drugs such as donepezil or rivastigmine, chemical warfare agents such as sarin, soman, tabun, and VX, and natural toxins such as galantamine and physostigmine [1-5]. These compounds irreversibly, pseudoirreversibly, or reversibly inhibit enzyme acetylcholinesterase (AChE) and/or butyrylcholinesterase (BChE) which causes accumulation of neurotransmitter acetylcholine with fatal consequences [6-11].

Analysis of neurotoxic inhibitors of cholinesterases and revealing their presence represents a substantial step in choosing a countermeasure aimed at risk reduction. The recognition of nerve agents and pesticides has major practical relevance for security purposes. Both AChE and BChE are suitable for the analyses as discussed previously [12]. Although AChE exerts a broader affinity for various

inhibitors, BChE is less sensitive to natural toxins. Biosensors based on BChE can provide a more accurate warning of nerve agents and cholinesterase-inhibiting pesticides than biosensors with AChE as a recognition element. The AChE biosensors are nevertheless a more common subject of research and various applications compared to the BChE biosensors and the role of BChE biosensors is quite underestimated. This review is focused on a survey of BChE biosensors, their development, applications, and a discussion of their advantages and disadvantages. Recent discoveries on BChE biosensors are cited in this review.

2. PRINCIPLE OF ELECTROCHEMICAL BCHE BIOSENSORS

An electrochemical biosensor with BChE works on a simple principle that contains at least two necessary steps. In the first step, an analyte with the enzyme BChE resulting in the blocking of its the activity. A high concentration of an analyte causes total blocking of BChE activity, while lower concentrations of an inhibitor do not reach all molecules of BChE and some activity remains. In the second step, the activity of BChE is determined properly. The chemical principles of electrochemical activity measurement are mentioned in the next text. The common principle of BChE biosensors is also valid for the biosensors with AChE, but the chemical methods for the activity assay have slight differences and some of them are not interchangeable. Because BChE has access to the active site of the enzyme in a wider and contains a lower number of aromatic amino acids, it is typically able to convert a higher number of substrates than AChE. BChE exerts good aryl acylamidase, esterase, and thioesterase activity on substrates with a large spectrum of molecular weights [13,14].

BChE is named after a substrate butyrylcholine according to the same logic that AChE is named after the neurotransmitter acetylcholine [15-17]. Compared with physiologically active acetylcholine, butyrylcholine is not a natural molecule, but an artificial substrate, giving the name of the enzyme with a high affinity to it. Furthermore, BChE is an enzyme with unknown physiological functions that are of practical relevance for the first phase of the detoxification reaction where it hydrolyzes some toxic compounds such as cocaine [18-20]. Hydrolysis of butyrylcholine by BChE releases butyric acid and choline as outputting products. Just the presence of butyric acid can be easily measured with a pH electrode as the pH of the medium drops [21]. The potentiometric assay of BChE activity can be an alternative method to standard spectrophotometric tests for the analysis of blood samples [22]. The potentiometric assay has a drawback in possibly reduced sensitivity when a highly buffered sample is analyzed and then the acidification is recorded until it exceeds the buffer capacity of the sample. On the other hand, the design is quite simple and allows the construction of biosensors based on ion-sensitive field effect transistors (ISFET). The principle of the BChE activity assay using a pH electrode is depicted in Figure 1.

BChE
H_2O
butyrylcholine
choline
butyrate
COO^-
H^+
detected by
a pH electrode

Figure 1. Measuring of BChE activity by pH electrode

The activity of BChE can be easily recorded by voltammetric methods when butyrylthiocholine is used as an enzymatic substrate. The principle of the reaction is simple but effective. Thiocholine cannot be easily oxidized, but once hydrolyzed by BChE into thiocholine and butyric acid, the thiol group is released. Thiocholine contains a free thiol group that is accessible to electrochemical oxidation that results in the formation of dithiocholine as the first stable product of the redox reaction [23,24]. The principle of this reaction is similar to the AChE assay for which acetylthiocholine can serve as a substrate and the second step based on thiocholine oxidation is identical [25,26]. BChE is, in addition, able to hydrolyze acetylthiocholine or acetylcholine; these substrates can be chosen instead of butyrylthiocholine or butyrylcholine. This approach was selected in some cases mentioned in the next chapters. The affinity of BChE is nevertheless higher to butyrythiocholine (butyrylcholine) than to acetylthiocholine (acetylcholine); hence, better analytical results can be expected when the esters of butyric acid are chosen for the assay purpose. However, acetylthiocholine was successfully tested as a substrate for BChE in various studies [27-30] and some types of BChE have slightly higher turnover rates for acetylthiocholine than for butyrylthiocholine [31]. The principle of an electrochemical assay based on butyrylthiocholine hydrolysis is depicted in figure 2.

BChE
H_2O
butyrylthiocholine
thiocholine
butyric acid
COOH
$-2H^+$ / -2e
applied voltage
detected current by voltammetry

Figure 2. Measurement of BChE by voltammetry using butyrylthiocholine as a substrate

The activity of BChE can be determined by using choline oxidase (ChOx) as a second enzyme. The first step of the assay is the same as that written in the text before devoted to potentiometric assay: Butyrylcholine is hydrolyzed by BChE into choline and butyric acid or butyrate depending on the pH of

the solution. In the second step, ChOx oxidizes choline to betaine, and hydrogen peroxide is released as a second product. Hydrogen peroxide can be simply detected by voltammetry, but optical detection is also possible when redox chromogenic reagents are added. The contemporary use of BChE and ChOx in biosensor construction was for instance chosen in the cited articles [32-35]. There is a similar ChOx-based assay of AChE activity with the use of acetylcholine as a substrate [36-38]. The principle of the BChE activity assay based on the combination with ChOx is summarized in Figure 3.

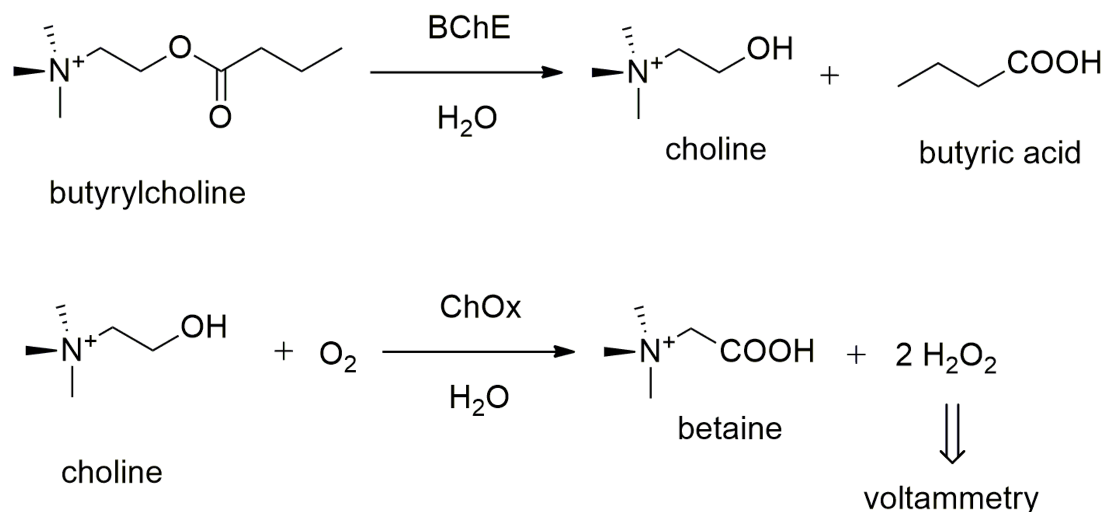

Figure 3. Measurement of BChE activity using ChOx followed by voltammetric detection of hydrogen peroxide

The electrochemical assays of BChE activity can be considered the most typical but they can occur in various adaptations and new, uncommon, types of BChE activity assays are also developed. Specific adaptations of the BChE activity assay are described in the chapter devoted to the examples of electrochemical BChE biosensors.

3. EXPECTED USE OF BChE BIOSENSORS AND COMPARISON WITH OTHER METHODS

Standard assay of neurotoxic pesticides, organophosphorus, or carbamate poisoning substances, and other similar compounds inhibiting AChE and/or BChE is based on instrumental analytical devices. The variant of gas chromatography (GC), liquid chromatography (LC), and capillary electrochromatography (CEC), and their combinations with mass spectrometry (MS) can be taken for common laboratory methods. They were extensively adapted for neurotoxic compound assays, including inhibitors of cholinesterases [39-47]. Instrumental analytical devices are suitable for an accurate and highly sensitive assay of neurotoxic compounds without inference from the other natural inhibitors of cholinesterases. Specific substances can be identified and quantified by the assay. Instrumental analytical devices are used as the first choice when an inhibitor of AChE and/or BChE should be proved in a sample. On the other hand, these devices are suited for laboratory conditions, but they are not suitable for assay performance in the field or other outdoor harsh conditions. The high costs for the acquisition

and service are another disadvantage. Trained and educated personnel in laboratories is another requirement for the successful performance of instrumental analytical devices.

Biosensors and chemosensors and various portable bioassays represent an alternative to the standard instrumental analytical devices; these devices are usually constructed as inexpensive analytical devices suited for the use of unskilled personnel and typically suitable for use in harsh outdoor conditions. Typical inhibitors of cholinesterases can be detected by three main types of biosensors. Biosensors based on AChE, biosensors with BChE, and biosensors with phosphotriesterases. Biosensors with AChE and BChE are based on the inhibition of enzyme activity by analyte and specificity of the whole biosensor outcomes from the selectivity of the enzyme to the specific inhibitor. Due to historical reasons, AChE biosensors became more widespread and many studies on them were performed. Some examples of these biosensors can be found in the references mentioned [48-53]. Both AChE and BChE biosensors will detect irreversible and pseudoirreversible inhibitors such as nerve agents, organophosphorus and carbamate pesticides, and other neurotoxic inhibitors covalently binding into the active site of the enzyme. The assays based on AChE and BChE are highly sensitive because one molecule of inhibitor stops the activity of the enzyme converting thousands of substrate molecules. The limits of detection exerted by AChE and BChE biosensors are typically quite low and sensitivity high. However, there are also some disadvantages. Neither of them can easily distinguish between the inhibitors. Moreover, various reversible inhibitors can also interact with cholinesterases and inhibit them; the problem is more related to AChE, which can be inhibited by a wide number of substances that are no or only weak inhibitors of BChE. The less developed aromatic gorge and peripheral anionic site at the entrance to the enzyme active site are in most cases responsible for the difference between AChE and BChE inhibition [54]. Compounds and elements such as caffeine [55], heavy metals [56,57], drugs such as galantamine, huperzine, and donepezil [58-60], and aflatoxins [61] can be mentioned. Therefore, the biosensor based on AChE can prove a wider number of inhibitors than the biosensors on BChE but reversible inhibitors can be considered as interferents when the biosensor is intended as an analytical tool for the demonstration of highly dangerous substances. In addition to electrochemical BChE biosensors, the enzyme can also be used for the construction of highly sensitive biosensors using a colorimetric, spectroscopic detection, or fluorescence assay [62]. The biosensors based on cholinesterases serve as disposable devices, and the biosensor that proved the presence of an inhibitor is not suitable for a repeated assay. Some works described recycling of the cholinesterase biosensor using oxime reactivators [63], and the reactivators can even serve as reagents to improve the assay by partially distinguishing between inhibitors [64]. However, the repeated use of a cholinesterase biosensor is questionable because hysteresis can be a problem in the assay. Low manufacturing costs further reduce the significance of protocols for recycling biosensors.

Other types of enzymes, including cholinesterases, can be chosen for the construction of a biosensor to analyze some neurotoxic inhibitors of cholinesterases. Enzyme phosphotriesterase also known as organophosphate hydrolase, paraoxonase, and aryldialkylphosphatase appears to be suitable for this purpose. The posphotriesterase biosensor was successfully tested for the analysis of organophosphorus neurotoxins in various studies [65-70]. There also exist other types of enzymes, and even some artificial enzyme-like structures can be used for the assay. The Zn2 + binding peptide can, for instance, developed for the same purpose as phosphotriesterase [71]. In comparison to the

cholinesterase biosensors, the biosensors based on phosphotriesterase are suitable for the assay of organophosphorus inhibitors only; the other neurotoxic inhibitors including carbamates, natural toxins, and others cannot be analyzed by these devices. It can be an advantage when higher specificity is desired. On the other hand, other compounds acting as substrates can interfere, but without significant neurotoxicity. Biosensors based on phosphotriesterase act in a simple stoichiometry, where one converted analyte makes a signal. There is no an amplification of signal like in the case of cholinesterases where one molecule of an inhibitor prevents the conversion of many molecules of cholinesterase substrate. The concept of a phosphotriesterase biosensor has a major advantage in the possibility of making continuous measurements where the presence of an analyte does not stop consecutive use of the biosensor. The survey of the aforementioned methods is given in Table 1.

Table 1. Methods for assay of neurotoxic compounds inhibiting cholinesterases

	Instrumental analysis	AChE biosensors	BChE biosensors	Phosphotriesterase biosensors
Suitability for outdoor use	no	yes	yes	yes
Costs	high	low	low	low
Sensitivity	high	high	high	medium or low
Identification of specific inhibitors	yes	no	no	no
Assay of irreversible and pseudoirreversible inhibitors	yes	yes	yes	no
Interference of natural inhibitors	no	yes	low	no or low
Repeated use	yes	no	no	yes
Suitable for untrained staff	no	yes	yes	yes

4. EXAMPLES OF ELECTROCHEMICAL BCHE BIOSENSORS

Electrochemical biosensors based on BChE were prepared in many adaptations. These biosensors were cheap and reliable devices in all of the described cases. Arduini and co-workers developed a biosensor in which BChE was immobilized on a carbon screen-printed electrode [72]. The biosensor worked according to the principle of chronoamperometry, in which the immobilized BChE used butyrylthiocholine as a substrate and the released thiocholine was oxidized by applied voltage + 300 mV against the Ag / AgCl reference electrode. The biosensor was tested for the paraoxon assay in olive oil samples. The aforementioned reaction was stopped when the paraoxon was present in the sample. The time of analysis for the pretreated samples was approximately half an hour. Paraoxon calibration exerted linearity in the concentration range of 20 to 100 ppb and a limit of detection of 6 ppb was reached. The authors also pointed out the fact that organic solvent can interfere with the assay when it reaches a high

concentration. Although 10 % v/v acetonitrile does not interfere, solutions with a concentration of acetonitrile above 20 % v/v kill nearly all of the BChE activity.

A paper-based chronoamperometric biosensor was developed for a contemporary assay of different groups of pesticides represented by paraoxon, 2,4-dichlorophenoxyacetic acid, and glyphosate inhibiting butyrylcholinesterase, alkaline phosphatase, and peroxidase [73]. The paper platform was designed as an origami with screen-printed electrodes on office paper and a filter paper pad containing the enzymes. The butyrylcholinesterase-mediated assay provided a limit of detection for paraoxon equal to 2 ppb and was suitable for performance in harsh field conditions. The paper sensor was plugged into a miniaturized potentiostat controlled from a smartphone. All reagents necessary for assay performance, including butyrylthiocholine, were soaked into the paper base and no elaborative manipulation with the biosensor or samples was necessary. The paper-based chronoamperometric biosensor was also used in the work by Cioffi et al. [74]. The biosensor was manufactured on office paper and contained Prussian blue, carbon black, and BChE. The assay had a limit of detection of 1.3 ng/ml and recovery between 90 and 110 % for paraoxon ethyl.

Paraoxon ethyl was also analyzed by another BChE biosensor [75]. The biosensor contained a paper-based screen-printed electrochemical sensor with carbon black Prussian Blue nanocomposite working electrode and immobilized BChE. Butyrylthiocholine served as the substrate, and thiocholine production was monitored chronoamperometry by its oxidation using an applied voltage of 300 mV against the Ag / AgCl reference electrode. Paraoxon ethyl inhibited BChE and stopped the reaction. The biosensor exerted a limit of detection of 3 μg/l and kept the activity of the BChE for at least 30 days when stored at 4 ° in a fridge.

A conductometric biosensor has been developed by Soldatkin and coworkers using three enzymes: AChE, BChE, and glucose oxidase [76]. The conductometric transducer had a size of 30 × 5 mm and contained 20 pairs of gold raster electrodes with dimensions 20 μm and an active surface area of 2 mm^2. The enzymes were immobilized on 30 nm gold nanoparticles. The measurement of BChE activity was found in the hydrolysis of butyrylcholine and the release of butyric acid caused an increase in conductivity which was recorded in the assay. The authors did not perform biosensors for specific analytes and the whole study was supposed to be the development of an assay platform. The BChE biosensor was sensitive to butyrylthiocholine as a substrate. The detection limit or other specifications for the substrate were not calculated. Taking into account the calibration curves, the limit of detection for butyrylthiocholine was less than 0.1 mmol/l.

The photoelectrochemical biosensor for organophosphorus pesticides was developed and tested for the malathion assay [77]. In the assay, the rolling-circle amplification technique is used as a way to reach low limits of detection and high sensitivity. The malathion interacts with an aptamer located on a DNA magnetic bead probe. The liberated single-stranded DNA probe can interact with the S-2-Au-BChE probe and be magnetically separated and washed. The separated complex with BChE hydrolyzed acetylthiocholine into choline and acetic acid. The accumulated thiocholine caused the dissolution of a nanoparticle containing MnO_2 on the CdS core, which was measured photoelectrochemically. The limit of detection for malathion was equal to 0.68 pg/ml. The principle of the assay is not common concerning the other biosensors, and the analyte does not directly interact with BChE. Malathion is also not an inhibitor of BChE. It can be oxidized to malaoxon before a standard inhibitory assay. The possibility of

analyzing such compounds is another advantage in addition to the high sensitivity. On the other hand, the assay also has some disadvantages. The high number of reagents used in the assay can complicate a manufacturing process. The specificity does not depend on BChE, but on the aptamer interacting with the analyte.

An assay with a BChE biosensor that works on the principle of nanoparticle dissolution was also developed for the dichlorvos assay [78]. BChE played a role as a biorecognition element in this study and the primary step of the assay was quite standard: acetylthiocholine was hydrolyzed by BChE to form thiocholine and butyric acid. Hydrolytically released thiocholine disintegrated nanoparticles composed of MnO_2 nanoflower – electron mediator. The free-electron mediator caused a change in the voltammetric characteristic of a sample. The reaction was stopped in the presence of dichlorvos. The assay exerted high sensitivity for the dichlorvos in the concentration range 10^{-10} – 10^{-6} mol/l and the detection limit of detection 3×10^{-10} mol/l. The survey of BChE biosensors with analytical descriptions and specifications is in Table 2.

Table 2. Electrochemical biosensors with immobilized BChE

Type of biosensor	*Analyte*	*Specifications*	*References*
Chronoamperometric biosensor with BChE bound on screen-printed electrode	paraoxon	linearity 20 to 100 ppb, and limit of detection 6 ppb, assay time approximately 30 minutes	[72]
Chronoamperometric biosensor with BChE in an origami paper-based screen-printed electrode	paraoxon	limit of detection 2 ppb	[73]
Chronoamperometric biosensor with Prussian blue, carbon black, and BChE on office paper	paraoxon ethyl	limit of detection is 1.3 ng/ml and recovery between 90 and 110 %.	[74]
Paper-based chronoamperometric biosensor with screen printed electrodes	paraoxon ethyl	limit of detection 3 μg/l	[75]
Conductometric biosensor with BChE immobilized on gold nanoparticles	no analyte, calibration for substrate butyrylthiocholine	limit of detection under 0.1 mmol/l	[76]
Photoelectrochemical biosensor with aptamer against analyte, BChE, DNA strand nanobeads, and MnO_2 CdSe nanoparticles	malathion	limit of detection 0.68 pg/ml	[77]

Voltametric biosensor with BChE and MnO_2 nanoflower–electron mediator	dichlorvos	concentration range 10^{-10} – 10^{-6} mol/l and limit of detection 3×10^{-10} mol/l	[78]

5. CONCLUSION

BChE biosensors are overshadowed by more widespread AChE biosensors. However, they are reliable analytical devices exerting some specifications, such as great sensitivity to various substrates, which selection can help prepare biosensors with the demanded specifications. Compared to AChE, BChE is not sensitive to inhibition to a such heterogenic group of inhibitors; therefore, results from an assay can be better interpreted. Recent papers on the construction of BChE biosensors confirmed the suitability of these devices for the assay of neurotoxic compounds and the possibility of preparing an inexpensive device with very low limits of detection and applicability in the field conditions at the same time. Further development of the BChE biosensors and an increase in their practical relevance can be expected in the future.

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