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Biosensor based on inhibition of monoamine oxidases A and B for detection of β-carbolines

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ABSTRACT

β-Carbolines are inhibitors of monoamine oxidases (MAO-A and MAO-B) and can be found in foods, hallucinogenic plant or various drugs. We have developed a fast analysis method for β-carbolines based on the inhibition of MAO. The enzymes were immobilized on screen-printed electrodes modified with a stabilized film of Prussian blue that contain also copper. We have used benzylamine as substrate for the enzymatic reaction and the hydrogen peroxide was measured amperometrically at −50 mV. The detection limits obtained were 5.0 μM for harmane and 2.5 μM for both harmaline and norharmane. The MAO-A is inhibited by all three tested β-carbolines (harmane, norharmane, and harmaline) while MAO-B is inhibited only by norharmane. The presence of norharmane in mixtures of β-carbolines can be identified based on the difference between the cumulative inhibition of MAO-A by all β-carbolines and MAO-B inhibition. The developed biosensors were used for food analysis.

1. Introduction

β-Carbolines such as harmane, norharmane, harmaline, etc. are a group of alkaloids possessing a tricyclic pyrido[3,4-b]indole ring with various substituents. They are naturally present in plants, animals and humans, but also significant quantities are found in tobacco smoke [1] or foods produced during cooking at high temperature, processing or smoking [2]. Rapid increase in plasma levels and high bioavailability of norharman and harman was found after consumption of β-carboline-containing foods or tobacco smoking [3]. The β-carbolines are inhibitors of monoamine oxidases (MAO) [4] and are psychoactive compounds found in "legal highs" [5] or hallucinogenic plant preparations such as ayahuasca [6]. In pharmacology, MAO-A selective inhibitor drugs are useful as antidepressants [7] and MAO-B selective inhibitor drugs are employed for treatment of Parkinson's disease [8], but dangerous interactions may appear, for example the foods rich in tyramine are contraindicated for the patients under MAO inhibitors medication: the "cheese effect" [9]. Consumption of β-carbolines rich foods (including drinking coffee) and smoking were associated with a protection against Parkinson's disease based on MAO inhibition [10], but excess consumption from various sources may lead to unpredictable neurochemical dysfunctions [11].

β-Carbolines are currently analyzed by various chromatographic or electrophoresis methods that are based on expensive equipments and require long and complicated extraction sample pretreatments [12]. The β-carbolines are electroactive compounds, but the carbon nanotubes based electrodes were used as detectors in chromatography [13] rather than standalone analytical devices. To the best of our knowledge, there are no reported alternative analytical methods-such as biosensors-for the selective, fast and low cost detection of β-carbolines in complex real samples. This paper presents the first developed electrochemical biosensor for the analysis of β-carbolines from food samples based on the inhibition of monoamine oxidase (MAO).

The physiological role of MAO is the oxidative deamination of biogenic monoamines (tyramine and neurotransmitters like dopamine or adrenaline, etc.) or potentially toxic exogenous amines [14]. The amines oxidation by MAO in the presence of oxygen leads to the production of hydrogen peroxide and the corresponding aldehyde. We have used an artificial substrate (benzylamine) for MAO. The enzymatic activity was determined by quantification of the production of hydrogen peroxide using screen-printed electrodes modified with Prussian blue with copper (PB–Cu). There are two isoforms of monoamine oxidase (MAO-A and MAO-B), distinguished by their differences in substrate and inhibitor selectivities. Numerous β-carbolines are reversible competitive inhibitors of MAO-A [4], but only norharmane is a specific inhibitor of MAO-B [15]. We have used the inhibitor selectivity of MAO-A/B for different β-carbolines to identify the presence of

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norharmane in a mixture of β-carbolines without separation of the analytes.

2. Materials and methods

2.1. Reagents

Monoamine oxidase (MAO, EC 1.4.3.4) from human recombinant type A (MAO-A; 120 UI/mg solid) and monoamine oxidase from human recombinant type B (MAO-B; 48 UI/mg) were provided by Sigma (Germany), stored at −20 °C in refrigerator and used as received. Analytical grade iron(III) chloride, potassium chloride, hydrochloric acid 37%, sodium phosphate dibasic, potassium phosphate monobasic, hydrogen peroxide 30%, citric acid, sodium hydroxide, sodium carbonate and boric acid were purchased from Sigma-Aldrich. Copper(II) sulfate anhydrous (98%) and potassium hexacyanoferrate(III) were obtained from Alfa Aesar and from Merck, respectively. Methyltrimethoxysilane (MTMOS) (Aldrich), tetramethoxysilane (TMOS) (Aldrich), HCl 37% (Merck), polyethylene glycol 600 (PEG 600) (Sigma) were used for the enzyme immobilization. 500 mM standard stock solution of benzylamine hydrochloride (Sigma, Germany) was prepared daily in distilled water. Working solutions of benzylamine were prepared in the electrochemical cell containing supporting electrolyte after baseline stabilization. Stock solutions of 5 mM harmane, norharmane and harmaline (Sigma, Germany) were prepared by dissolving the corresponding amount of each inhibitor in methanol. The phosphate buffer solution 0.05 M (PBS) with pH 7.38 supplemented with KCl 0.1 M was prepared with Milli-Q ultrapure water (Millipore).

2.2. Apparatus

The amperometric measurements were performed with a galvanostat/potentiostat Autolab PGSTAT302N (Metrohm-Autolab) controlled by a PC with the software Nova 1.8. The screen-printed electrodes were produced by DropSens (Spain) on a ceramic substrate (producer code DS-110). The screen-printed electrodes have a round working electrode with a diameter of 4 mm, an auxiliary electrode (both WE and AE are made with carbon based ink) and a Ag/AgCl pseudorefecence electrode. The electromagnetic noise produced by magnetic stirring was reduced with the filter from the ECD module set to 1 s.

2.3. Prussian blue–copper mixture (PB–Cu) deposition

The screen-printed carbon electrode was introduced in 6 mL cell with a freshly prepared solution containing 0.5 mM $FeCl_3$, 0.25 mM $CuSO_4$ and 0.5 mM $K_3Fe(CN)_6$ in 10 mM HCl and 100 mM KCl. The PB–Cu film was formed on the electrode surface by cyclic voltammetry (20 cycles between −0.1 V and 0.5 V at a scan rate of 50 mV/s). The modified electrodes were dried at room temperature for at least 1 h before use. For comparison, electrodes with PB without Cu were produced using a similar protocol from a solution without 0.25 mM $CuSO_4$.

2.4. Enzyme immobilization

The immobilization of MAO on the PB–Cu screen-printed electrodes was carried out according to a procedure previously described [16], the entrapment in sol–gel being a biocompatible method that allows the co-immobilization of stabilizers and optimization of the matrix properties aiming both an appropriate environment for enzyme and good mass transport of substrate or inhibitors [17]. The sol–gel precursor solution (solution A) was prepared from 44 μL of H_2O, 40 μL of 1 mM HCl, 10 μL of TMOS, 5 μL of MTMOS and 5 μL of PEG 600 and let to hydrolyze overnight at 4 °C. A 3% (m/v) solution of hydroxyethyl-cellulose (HEC) medium viscosity was prepared in 3 mL water by magnetically stirring the mixture for few hours and then 0.45 g of graphite was added (solution B). 10 μL of MAO-A enzyme solution or 7 μL of MAO-B enzyme solution diluted with 3 μL PBS were mixed with 5 μL of solution B and kept under ice for 10 min. Then, 10 μL of solution A were added on the mixture. 3.5 μL from the final solution were rapidly spread onto screen-printed carbon electrodes modified with PB–Cu film. Final enzymatic activity was of 0.17 UI on each MAO-A biosensor, respectively of 0.21 UI for MAO-B biosensor. The electrodes were dried about 1 h at room temperature and then kept in a desiccator at 4 °C.

2.5. β-Carbolines analysis

The amperometric measurements of the immobilized enzymatic activity were made at −50 mV in 6 mL magnetically stirred PBS. The current intensity was recorded and, after current stabilization, 5 mM benzylamine (final concentration in the cell) was injected. The time necessary to reach the plateau was less than 1 min. The difference of the current intensity between the baseline and the plateau was measured and is correlated with the activity of the immobilized enzyme. The cell was washed with distilled water between measurements. In the first step, the initial response of the electrodes was measured (I_0), then electrodes were incubated for 10 min in 6 mL stirred standard or sample solutions and the remaining enzymatic activity (I_1) was measured by injecting the substrate in the sample. The percentage of inhibition ($I\%$) was determined according to the following formula: $I\% = ((I_0 - I_1)/I_0) \times 100$ and correlated with the concentration of β-carbolines. The biosensors were regenerated by incubation in PBS solution for 5 min and finally, the enzymatic activity was measured again and should be equal with the initial activity (I_0). One biosensor can be used for up to 7 inhibition measurements.

2.5.1. Real sample analysis

β-Carbolines were determined in various food samples from a local store: unroasted green coffee, smoked fish (sprat), chicken ham and green tea. First, the food samples were crushed in a mortar and ~0.5 g were weighted in 2 mL Eppendorf tubes. Then, 1.5 mL of 10 mM NaOH was added over of each sample and the solution was vigorously mixed. The resulted solution was centrifuged and the liquid was discarded. Subsequently, the solid residue was mixed with 1 mL of borate buffer pH 10.59 (boric acid–sodium carbonate) followed by centrifugation and liquid discarding. Both these extraction steps were used to remove the biogenic amines that may be substrate for MAOs. The β-carbolines were extracted with 1 mL of ethyl acetate and the solvent was evaporated [13]. Finally, the β-carbolines were recuperated in 1 mL methanol. The same β-carbolines were analyzed by injecting between 20 and 150 μL from the resulted methanol solution in the amperometric cell following the optimized procedure. The samples were analyzed directly or spiked with known concentrations of β-carbolines (before extraction).

3. Results and discussions

3.1. PB–Cu film formation onto screen-printed carbon electrodes

The Prussian blue mediator is very sensitive towards hydrogen peroxide, but suffers from low stability at neutral and weakly basic pH [18]. Various strategies have been proposed for the stabilization of Prussian blue such as deposition in the presence of surfactants [19], creation of analog compounds with other metals

such as copper, cobalt and nickel [20] or multiple layers of Prussian blue and analog compounds [21]. We have electrodeposited a mixed PB–Cu film on the screen-printed carbon electrode from a solution that contains $FeCl_3$ together with $CuSO_4$ into 0.5 mM $K_3Fe(CN)_6$, 10 mM HCl and 100 mM KCl. Different ratios of $FeCl_3$, $CuSO_4$ and $K_3Fe(CN)_6$ (1:1:1; 0.5:0.5:1 and 1:0.5:1) were tested in order to obtain a stable film of PB–Cu, a good sensitivity towards H_2O_2 detection and to reduce the background noise. A mixture of 0.5 mM $FeCl_3$, 0.25 mM $CuSO_4$ and 0.5 mM $K_3Fe(CN)_6$ was chosen as optimum for the biosensor development. The formation of PB–Cu film was carried out by 20 cycles and increasing peaks at +0.096/0.020 V were observed (Fig. S1).

3.2. PB–Cu film characterization

The voltammetric parameters for PB–Cu film after the complete formation (20 cycles) measured in electrolyte solution (10 mM HCl and 100 mM KCl) at a scan rate of 0.05 V/s are $E_{ox}=0.096$ V, $E_{red}=0.020$ V, $\Delta E_p=0.078$ V, $I_{ox}=0.169$ mA, $I_{red}=-0.173$ mA, $I_{ox}/I_{red}=-0.976$. The surface coverage with PB–Cu is 0.309×10^{-9} mol/cm^2 calculated from the anodic peak and 0.301×10^{-9} mol/cm^2 from the catodic peak. The calculated thickness of PB–Cu film is 0.453 nm [19]. For comparison, the CV recorded using the PB electrodes obtained without Cu has the following characteristics: $E_{ox}=0.086$ V, $E_{red}=0.005$ V, $\Delta E_p=0.080$ V, $I_{ox}=0.103$ mA, $I_{red}=-0.131$ mA, $I_{ox}/I_{red}=-0.786$.

Cyclic voltammetry between −0.1 and 0.5 V and amperometry at −50 mV were used to verify the stability of the formed film of PB–Cu and compared with PB at pH 7.38. The stability evaluated by CV was calculated as peak high decrease after immersion in unstirred electrolyte solution for different periods of time (10 min, 20 min, 30 min, 1 h and 2 h). In Fig. 1 are presented the cyclic voltammograms registered after the deposition step and after 2 h for PB–Cu and PB electrodes. As it can be seen, the cyclic voltammogram registered after 2 h was overlapped with the other one registered after the deposition step at pH 7.38 for Cu–PB. Also, the stability of the Cu–PB film was not affected by the deposition of the sol–gel enzymatic layer. The CV recorded for PB electrodes showed a 23% decrease of the peak intensity after 2 h immersion in buffer in comparison with the initial peak height.

The stability of the PB–Cu film at pH 7.38 was also verified by amperometry at −0.05 V. Amperometric measurements were made for repeated injections of 5 μM H_2O_2 ($n=10$) followed by the electrode washing after each measurement. Then the modified electrode was immersed for 10 min in the electrolyte solution followed by another set of 10 amperometric measurements. This amperometric testing procedure was repeated during a period of 2 h. An average value (nA) of the signals was calculated for each set of 10 amperometric measurements. A good reproducibility was obtained when the amperometric measurements were made in a PBS pH 7.38 (RSD of 3.1%, $n=10$ measurements, for PB–Cu and 2.3% for sol–gel–PB–Cu electrode). The signal variation at pH 7.38 during the 2 h was less than 5% for both modified electrodes: PB–Cu and PB–Cu covered with sol–gel. In the case of the sol–gel–PB–Cu the amperometric signals for the same concentration of H_2O_2 were slightly lower comparative with the signal measured with a PB–Cu electrode (e.g. for 5 μM H_2O_2, the signals obtained with sol–gel–PB–Cu and PB–Cu electrodes were 73.6 ± 2.2 nA and 84.0 ± 2.8 nA, respectively). Calibration plots obtained at pH 7.38 were linear in the domain between 1 and 105 μM H_2O_2 by using both modified electrodes: PB–Cu and sol–gel–graphite–PB–Cu and the signals are higher than for PB, but this phenomenon may be due to a higher mediator loading (Fig. S2). The signals recorded with PB electrodes used for comparison decreased by 30% after immersion in PBS for 2 h (from 74.2 nA to 52.2 nA) and this confirms the stabilization of PB by Cu.

3.3. Choice of substrate concentration

One important factor with major influence on the analysis performances based on enzymatic inhibition is the optimization of the substrate concentration. Usually, the measurements of the enzymatic inhibition use a high substrate concentration in order to have an important analytical signal that is reduced by the inhibitor. For this the calibration curves for benzylamine were determined for both biosensors with MAO-A/B and they have the normal shape: a linear part followed by a plateau (Fig. 2). The calibration graphs for substrate were linear between 1 and 10 mM benzylamine for MAO-A and 0.5–10 mM for MAO-B. In our case,

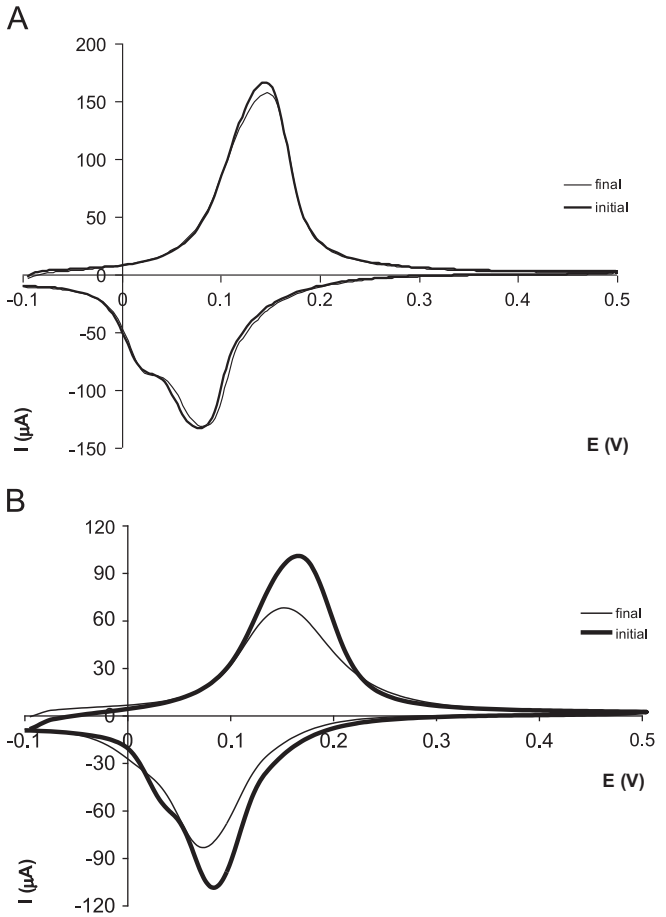

Fig. 1. Cyclic voltammograms recorded initial and after 2 h immersion in PBS pH 7.38 using PB–Cu electrodes (A) and PB electrodes (A).

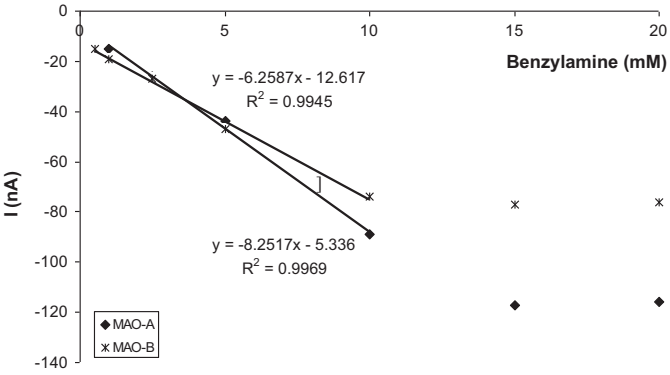

Fig. 2. Calibration graphs for benzylamine obtained with MAO-A and MAO-B biosensors.

the inhibition of MAOs by β-carbolines is competitive and fast reversible [22]. In consequence, higher substrate concentrations imply a lower inhibition percentage for the same inhibitor concentration [23].

We have studied the influence of the substrate concentration on inhibition percentage measured for 7.5 μM norharmane with MAO-A biosensors. An important decrease of the inhibition percentage with the increase of the substrate concentration was observed. Thus, for 20 mM benzylamine the inhibition percentage is only 39% a value significantly smaller in comparison with 59% that is obtained using 5 mM benzylamine (Fig. 3). On the other hand, an analytical signal that is sufficiently important is required for inhibition measurements, so a compromise is required. In consequence, 5 mM benzylamine was used in subsequent studies.

3.4. Inhibition of MAOs by solution containing a single β-carboline

The response of the biosensors for substrate was evaluated before inhibition measurements. The RSD for substrate detection was calculated for the same electrode or different electrodes. The RSD calculated for the same electrode was 6.08% for a concentration of 5 mM benzylamine ($n=20$; MAO-A). The RSD for different electrodes was 6.4% for a concentration of 5 mM benzylamine ($n=10$). The reproducibility of the inhibition process calculated for a standard solution of 7.5 μM norharmane was 5.5% ($n=7$) for a single biosensor and 6.1% ($n=5$) for different MAO-A biosensors. The biosensors can be regenerated after an inhibition by incubation in PBS because the inhibition is reversible. The operational stability of the biosensor is very good: one biosensor can be used for up to 7 successive inhibition measurements, which implies also 35 measurements of the immobilized enzyme activity.

The influence of the inhibition time was studied for both MAOs and all three tested β-carbolines (only norharmane was studied using MAO-B biosensors because harmane and harmaline do not inhibit this isoform). The inhibition percentages increase significantly with the time for all couples enzyme-inhibitor (Fig. 4). We have chosen a 10 min inhibition time for future experiments as a compromise between good detection sensitivity and a reasonable analysis time.

Calibration graphs for inhibition based biosensors consist of a linear part and a plateau that start at an inhibition percentage around 80%. The limit of detection was considered the concentration that induces an inhibition percentage of 15% (a values that is three times bigger that the RSD of the substrate measurements). Detection limits obtained for norharmane were 2.5 μM for biosensors based on both MAO-A and MAO-B. The detection limits obtained using biosensors based on MAO-A were 5.0 μM for harmane and 2.5 μM for both harmaline and norharmane. The

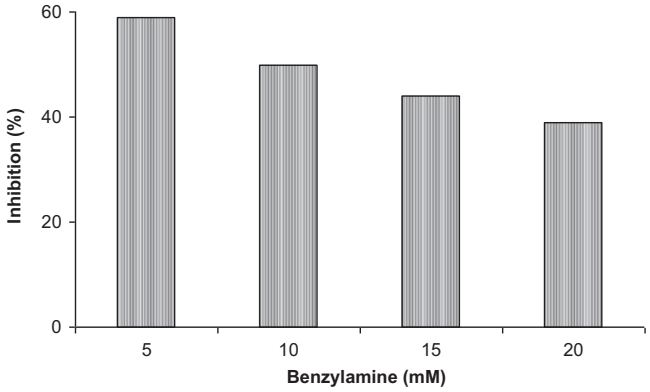

Fig. 3. The influence of the substrate concentration on the MAO-A inhibition by 7.5 μM norharmane.

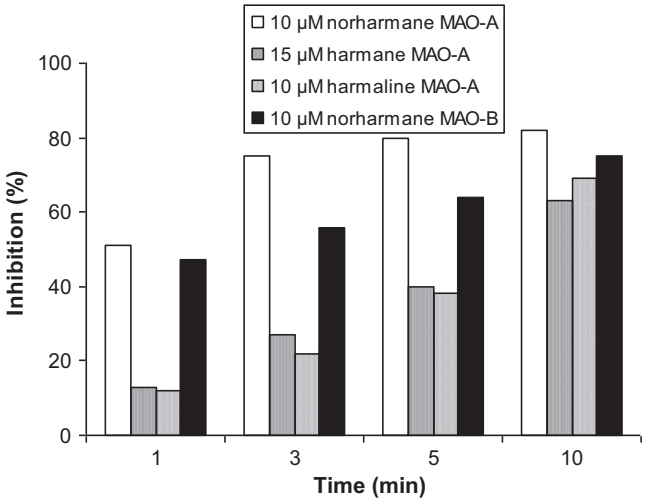

Fig. 4. Influence of the incubation time on the inhibition percentage measured with MAO-A and MAO-B biosensors.

Table 1
Characteristics of the calibration graphs.

Name of inhibitor	Concentration domain (μM)	Linear concentration domain (μM)	Equation	R^2
MAO-A biosensor				
Norharmane	2.5–30	2.5–10	8.48x–7	0.9843
Harmane	5–30	5–13	6.4x–14	0.9884
Harmaline	2.5–30	2.5–10	6.52x+3.5	0.9820
MAO-B biosensor				
Norharmane	2.5–30	2.5–10	8x–4	0.9881

concentrations of β-carbolines that induce a 50% inhibition for biosensors based on MAO-A are 6.7 μM for norharmane, 10 μM for harmane and 7.2 μM for harmaline, while MAO-B biosensors have an inhibition percentage of 50% for 6.8 μM norharmane. The characteristics of the calibration graphs are listed in Table 1.

The sensitivity of the analysis based on enzymatic inhibition is directly correlated with the inhibition constant (k_i), but there are also other factors that influence the performance of the biosensors besides the specific interaction between enzymes and inhibitors such as the diffusion from the solution into the sol–gel matrix where the enzyme is immobilized. In good agreement with our results, the reported k_i of MAO-A and MOA-B by norharmane are relatively similar and smaller than the k_i of MAO-B by harmane [22].

3.5. Inhibition of MAOs by mixtures of β-carbolines

The inhibition of MAO-A biosensors by mixtures of two β-carbolines was studied by selecting two different concentrations from the calibration curves: a lower one that produced an inhibition around 20% and a higher one that produced an inhibition around 40%. It was observed that the inhibition percentages were higher for mixtures in comparison with the single inhibitor, but the inhibition percentage is not additive. Thus, for norharmane and harmaline was obtained an inhibition percentage of 34% for the mixture of the lower concentration, while the sum of the individual percentages is 39%. Also, the inhibition produced by a lower concentration with a higher one produced an inhibition of 53% while the sum of the individual percentages is 59%. The results obtained with MAO-A biosensors are presented in Table S1.

Table 2
Real samples analysis.

Sample	MAO-A biosensor μg norharmane/g sample ± SD	MAO-B biosensor μg norharmane/g sample ± SD	MAO-A biosensor Recovery (%)	MAO-B biosensor
Green coffee (unroasted)	n.d	n.d	–	–
Green coffee (unroasted) spike with 201.6 μg/ g sample norharmane	218 ± 15	222 ± 14	108.2	110.1
Smoked fish (sprat)	n.d	n.d	–	–
Smoked fish (sprat) spike with 201.6 μg/g sample norharmane	217 ± 12	199.6 ± 12	107.8	99.0
Cheese	n.d.	n.d.	–	–
Chicken ham	n.d.	n.d.	–	–
Green tea	n.d.	n.d.	–	–

n.d. – not determined (under LOD);
SD – standard deviation.

The MAO-B is inhibited only by norharmane. The other two studied β-carbolines do not inhibit this isoform even at high concentrations and do not influence the inhibition by norharmane. Thus, the inhibition recorded for standard solutions of 7.5 μM norharmane is similar with the ones measured for mixtures of 7.5 μM norharmane + 100 μM harmane and 7.5 μM norharmane + 100 μM harmaline.

Usually, the biosensors based on enzymatic inhibition are able to detect the global presence of all the inhibitors in the sample reported as an inhibition percentage equivalent with a reference compound and not to identify each individual inhibitor. The differences between the inhibition percentages produced by different inhibitors on several enzyme isoforms may be used for the creation of an artificial neural network (ANN) that can discriminate between different analytes: e.g. two microcystin variants (LR and YR) were analyzed from mixtures using the differences in inhibition percentages measured with a mutant and the wild type protein phosphatase [24]. Even easier, the presence of an inhibitor can be discriminated in complex samples when only one enzyme is inhibited by the analyte: e.g. omethoate was identified using two acetylcholinesterase biosensors – one based on sensitive enzyme extracted from *Drosophila melanogaster* and the other based on omethoate-resistant enzyme extracted from electric eel [25]. Similarly, our system based on two MAOs is able to identify the presence of norharmane in a mixture of β-carbolines or indicate the differences between the inhibition percentages induces on MAO-A and MAO-B, an important information because the pharmacological effects are related with inhibited isoform [26].

3.6. Determination of β-carbolines in food samples

The enzymatic biosensors may suffer from two types of interferences: (1) electrochemical substances that may be oxidized/reduced by the electrode and (2) non-specific enzymatic substrates or inhibitors. The electrodes modified with PB are known to have good anti-interferences abilities due to their operation at low overpotentials that allow the quantification of H_2O_2 in the presence of easily oxidizable substances usually found in biological samples [27]. We have confirmed the absence of electrochemical interferences by injection of samples extract in the absence of MAOs and we have observed no signal. The MAOs catalyze the oxidation of numerous amines, but we have used a two steps extraction protocol to avoid the presence of biogenic amines. We did not obtained any signal at the injection of sample extracts and thus we confirm the absence of interferences caused by enzymatic substrates. The other inhibitors of MAOs besides β-carbolines are drugs (see Section 1) or numerous synthetic substances that are drug candidates such as benzimidazole and caffeine analogs [28] that are not present in food samples.

The total contents of β-carbolines found in real samples are expressed in μg norharmane/g sample and they were calculated with both MAO-A and MAO-B biosensors. The results are presented in Table 2. We did not detect β-carbolines in the analyzed food samples. We attribute the absence of β-carbolines in smoked fish to the industrial preparation using commercial buffered smoke instead of traditional methods that contains significant lower concentrations of all heterocyclic aromatic amines [29]. The recovery percentages of the spiked norharmane are between 99% and 110%.

We presented the first biosensors developed for the analysis of harmane, norharmane or harmaline based on the inhibition MAO-A and MAO-B. Interestingly, the inhibition is fast reversible and thus the biosensors can be reused for up to seven analyses. Based on cumulative inhibition of MAO-A by all β-carbolines and the fact that MAO-B is inhibited only by norharmane we were able to discriminate the presence of norharmane in mixtures of β-carbolines. The proposed biosensors can be applied for the analysis of foods or other samples such as drugs or legal highs.

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Appendix A. Supplementary information

Supplementary information associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.talanta.2015.02.013.

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