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Electrochemical DNA Biosensors – Useful Diagnostic Tools for the Detection of Damage to DNA Caused by Organic Xenobiotics (A Review)

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Abstract: Supramolecular interactions of various organic xenobiotic compounds with DNA are among the most important aspects of biological studies in clinical analysis, drug discovery, and pharmaceutical development processes. In recent years, there has been a growing interest in the electrochemical investigation of interactions between studied analytes and DNA. Observing the pre- and post-electrochemical signals of DNA or monitoring its interaction with xenobiotics provides good evidence for the interaction mechanism to be elucidated. Such interaction can also be used for sensitive determination of these compounds. This short review should provide evidence that the electrochemical approach brings new insight into human health protection or rational drug design and leads to further understanding of the interaction mechanism between organic xenobiotic compounds and DNA.

Keywords: Supramolecular chemistry; DNA biosensors; DNA damage detection; Review.

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Introduction

In the last decade, increasing attention has been paid to the binding of small organic molecules to nucleic acids. Such *in vitro* studies have a key importance for detailed understanding to these supramolecular interactions, especially in terms of damage to DNA caused by various xenobiotic compounds [1].

A variety of small molecules are known to interact reversibly with double-stranded DNA (dsDNA) through one of the following three modes: (i) electrostatic interactions with the negatively charged nucleic sugar-phosphate structure, (ii) groove binding interactions, or (iii) intercalations between the stacked base pairs of dsDNA [2-4].

Analysis of the interfacial biomolecular interaction between DNA-targeted drugs and immobilized DNA probes has a particular role in the rational design of novel DNA-binding drugs and to the drug screening. Interactions of anticancer drugs with nucleic acids have been studied by numerous physical and biochemical techniques. Nuclear magnetic resonance, spectrophotometry, vibrational spectroscopy (Fourier transform infrared spectroscopy and Raman spectroscopy), light scattering studies, surface plasmon resonance, viscometry, electric linear and circular dichroism, or capillary electrophoresis have been applied to provide insight into binding modes, DNA affinity, and base pair selectivity of DNA-binding drugs [5]. However, these techniques mostly address the issues of the binding mechanisms and structural analysis (*e.g.*, DNA base sequence selectivity, correlation of structure–activity relationships, linkages between the geometry and thermodynamic properties, or influences of substituent modifications on the physical, chemical, and biological properties of the formed drug–DNA complex) [6].

Nucleic acid layers combined with electrochemical transducers have produced a new kind of affinity biosensor capable of rapidly recognizing and monitoring DNA-binding organic compounds [1]. Electrochemical biosensors have been successfully used for a number of applications including the monitoring of DNA damage, studies of the interactions of DNA with various genotoxic agents (such as carcinogens, mutagens, toxins, or pharmaceuticals and drugs), and also for the detection of specific mutations in DNA sequences [7]. Thus, they potentially offer fast and inexpensive alternative to traditional methods of measuring analyte–DNA interactions [8-10].

Recently, various reviews of electrochemical DNA biosensors have been reported [1,11-16]. The present review will focus on the most widely used strategies in the technology of electrochemical DNA biosensors, with the special emphasis placed on their construction and application in the field of DNA damage detection and investigation of supramolecular interactions between organic xenobiotic compounds and DNA.

Electrochemical DNA Biosensors for the Detection of DNA Damage

DNA belongs to main biological macromolecules that undergo serious structural changes such as oxidation of the DNA bases and sugar moieties and/or release of the bases as well as strand breaks caused by chemical systems generating so-called reactive oxygen (ROS), reactive nitrogen (RNS), or reactive sulfur (RSS) species [17,18] and by other classes of genotoxic substances [19]. Thus, one of the main application areas for DNA biosensors is detection of damage to DNA. ROS are formed either endogenously (during normal aerobic metabolism and under various pathological conditions) or exogenously (*e.g.*, upon exposure to UV light, ionizing radiation, environmental mutagens and carcinogens). About ten-thousands to millions DNA damage events occurs to a cell per day [19]. Accumulation of oxidative DNA lesions is associated with aging and with a variety of human diseases including cancer and neurodegeneration.

Altered chemical, physicochemical, and structural properties of damaged DNA are reflected in its redox behavior, which is utilized in numerous techniques of DNA damage detection. Electrochemical DNA biosensors have been used not only to detect but also to induce and control DNA damage at the electrode surface via electrochemical generation of the damaging (usually radical) species [20]. In this way, drugs and chemical carcinogens (*e.g.*, adriamycin [21], niclosamide [22], nitrofurazone [23], and nitro derivatives of polycyclic aromatic hydrocarbons [24]) have been investigated.

Construction of the Biosensors

DNA biosensors are integrated receptor–transducer devices that use DNA as a biomolecular recognition element to measure specific binding processes with DNA, usually by electrical, thermal, or optical signal transduction [12]. Compared with other transducers, electrochemical ones received particular interest due to a rapid detection and great sensitivity. Amongst the electrochemical transducers, carbon-based electrodes (*e.g.*, glassy carbon electrode (GCE), pyrolytic graphite electrode (PGrE), carbon paste electrodes (CPEs), carbon film electrodes (CFEs), screen-printed carbon electrodes (SPCEs), or carbon nanoparticles modified electrodes) exhibit several unique properties. The wide electrochemical potential window in the positive direction allows sensitive electrochemical detection of oxidative damage caused to DNA by monitoring the appearance of oxidation peaks of DNA bases [25].

Adsorption is the simplest method to immobilize DNA on an electrode surface. It does not require reagents or special modifications in the DNA structure. There are many reports on DNA immobilization using a potential applied to GCEs, CPEs, or SPCEs [1,26-28]. The smoothed surface of the carbon electrode is usually pretreated by applying a positive potential (*ca.* 1.5 to 1.8 V *vs.* Ag|AgCl) for a certain time. This pretreatment of the carbon surface increases its roughness and hydrophilicity [29,30]. Afterwards, the electrochemical adsorption of DNA is realized using a stirred solution at a potential of 0.5 V (*vs.* Ag|AgCl) for a preset time that depends on DNA concentration. This potential enhances the stability of the immobilized DNA through the electrostatic attraction between the positively charged carbon surface and the negatively charged hydrophilic sugar-phosphate backbone [20].

Another way to immobilize DNA by adsorption on an electrochemical transducer has been described [31,32]. In this case, the DNA biosensor was prepared by dipping a GCE in a DNA solution and leaving the electrode to dry. This sensor was then used to preconcentrate nitroimidazole [31] or mitoxantrone [32] on the surface and to study the interaction mechanism of these drugs with DNA by means of cyclic voltammetry (CV), differential pulse voltammetry (DPV), and square wave voltammetry (SWV).

Different approach for immobilization of DNA is based on utilizing a GCE in the role of a transducer [33]. The DNA-modified electrode was prepared by the evaporation of a small volume of DNA solution on the electrode surface. Similarly, an electrochemical DNA biosensor has been developed [34], based on DNA adsorbed on a polished basal plane PGrE. An adsorptive method to immobilize DNA on the gold electrode (AuE) has also been reported [35,36]. AuE was modified by dropping a small volume of DNA on its surface and air-drying overnight and rinsing to remove unabsorbed DNA followed.

DNA-modified mercury electrodes can be prepared easily by immersing a hanging mercury drop electrode (HMDE) or a mercury film electrode (MFE) into a drop of the DNA solution. This approach requires less amount of DNA for analysis [37-39]. DNA bases and nucleosides are strongly adsorbed at mercury electrodes. Nucleosides possess an extraordinary ability of self-association (two-dimensional condensation) at the surface of mercury electrodes and can form monomolecular compact films. At high positive potentials, all DNA bases can react with mercury electrodes forming sparingly soluble compounds.

Nanostructured interfaces between the bare electrode and DNA, formed by various nanomaterials like gold nanoparticles and carbon nanomaterials (*e.g.*, single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs), carbon nanofibers, graphene (Gp) and graphene oxide (GpO) nanosheets) [40-49], represent another approach to

the enhancement of the biosensor response due to inherent electroactivity, effective electrode surface area, *etc.* [50,51]. Nanometer scale complex films of DNA, enzymes, polyions, and redox mediators were suggested for tests of genotoxic activity of various chemicals [52].

Detection Techniques

Voltammetric (especially cyclic voltammetry (CV), differential pulse voltammetry (DPV), and square wave voltammetry (SWV) (Fig. 1)) and chronopotentiometric (CP) detection modes are most frequently used [25]. Together with them, electrochemical impedance spectroscopy (EIS) (Fig. 2) becomes to be popular at DNA-based biosensors [53]. According to electrochemically active species, which responses are evaluated at the detection of damage to DNA, the experimental techniques can be classified as follows [12]:

a) label-free and often reagent-less techniques which represent the work with no additional chemical reagents (redox indicators, mediators, enzyme substrates, *etc.*) needed to generate measured response,
b) techniques which employ redox indicators either non-covalently bound to the DNA (groove binders, intercalators, anionic or cationic species interacting with DNA electrostatically) or presents in the solution phase (*e.g.*, hexacyanoferrate anions),
c) techniques which employ electrochemically active labels (nanomaterials, enzymes, *etc.*) covalently bound to DNA (not frequently used in fundamental investigations of DNA damage).

Combination of these principles allows to obtain more complex information on DNA changes and damaging supramolecular interactions, as well [51,54].

The first group of techniques utilizes surface activity or redox activity of DNA itself [55]. The electrochemical activity is based on the presence of redox active sites at nucleobases and sugar residues. Only DNA bases can undergo redox processes at carbon and mercury electrodes. Deoxyribose and phosphate groups are not electroactive. Electrochemical oxidation on carbon electrodes [56,57] showed that all bases (guanine, adenine, cytosine, and thymine) can be oxidized, following a pH dependent mechanism. Electrochemical preconditioning of the GCE enabled a better peak separation and an enhancement of the current of the oxidation peaks for all four DNA bases in phosphate buffer of pH 7.4 (value close to physiological pH) used as the supporting electrolyte [57].

Electrochemical reduction of natural and biosynthetic nucleic acids at a dropping mercury electrode (DME) [1,3,58] showed that adenine and cytosine residues as well as

guanine residues in a polynucleotide chain are reducible. The CV of DNA at a HMDE showed a cathodic peak due to irreversible reduction of cytosine and adenine moieties. The reduction of guanine moiety occurs at very negative potentials but a peak due to the oxidation of the reduction product of the guanine moiety (7,8-dihydroguanine moiety) could be detected in the reverse scan [3].

As both the electrochemical reduction and oxidation of DNA bases are irreversible, measurements cannot be performed repeatedly. Initial increase in the anodic guanine moiety response after short-time incubation of the biosensor in damaging agents can indicate opening of the original dsDNA structure, while decrease in this response (Fig. 1) is an evidence for the

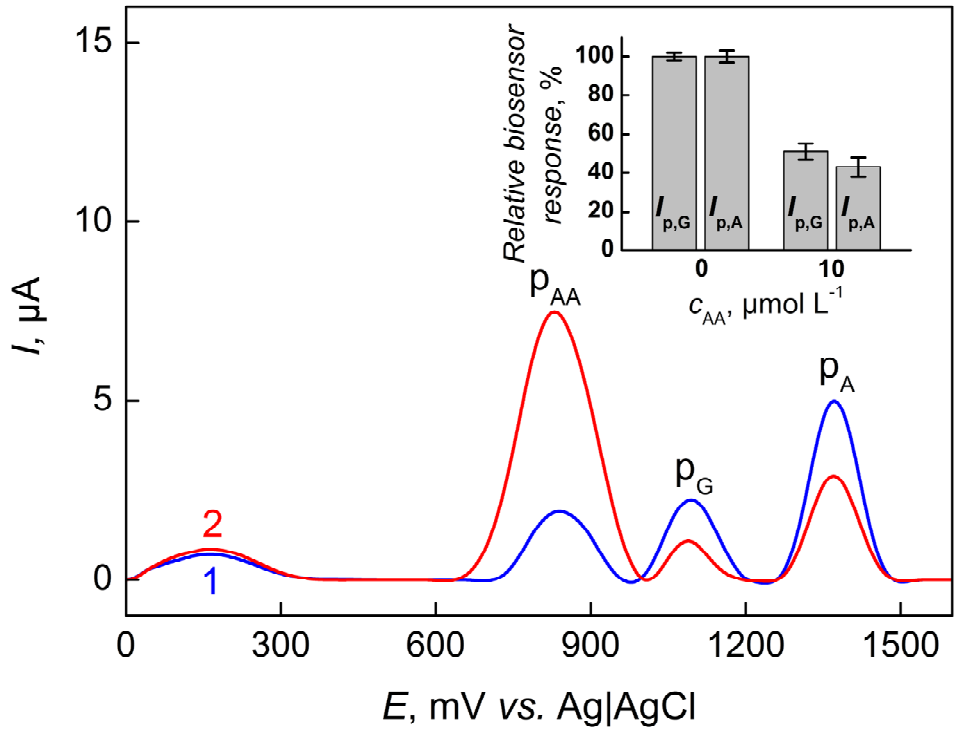

Fig. 1: *Baseline-corrected square wave voltammograms recorded in 0.1 mol L^{-1} acetate buffer of pH 4.8* [59]. Legend: (**1**) measured at a DNA-modified GCE after 5 min incubation of the biosensor in 0.1 mol L^{-1} phosphate buffer of pH 7.0 and (**2**) measured at a DNA-modified GCE after 5 min incubation of the biosensor in 0.1 mol L^{-1} phosphate buffer of pH 7.0 containing 1×10^{-5} mol L^{-1} 2-aminoanthracene (AA); $\mathbf{p_G}$ ... peak of a guanine moiety, $\mathbf{p_A}$ ... peak of a adenine moiety, $\mathbf{p_{AA}}$ ... mixed peak of intercalated AA and interference from the adsorbed DNA. Experimental conditions: polarization rate 3 V s^{-1}, pulse amplitude 0.04 V, frequency 200 Hz, potential step 0.015 V. Inset: the relative biosensor responses to DNA damage caused by AA, evaluated from the changes in the height of the guanine ($I_{p,G}$) and adenine ($I_{p,A}$) moiety peaks; the error bars are constructed for the significance level of 0.05 (n = 3).

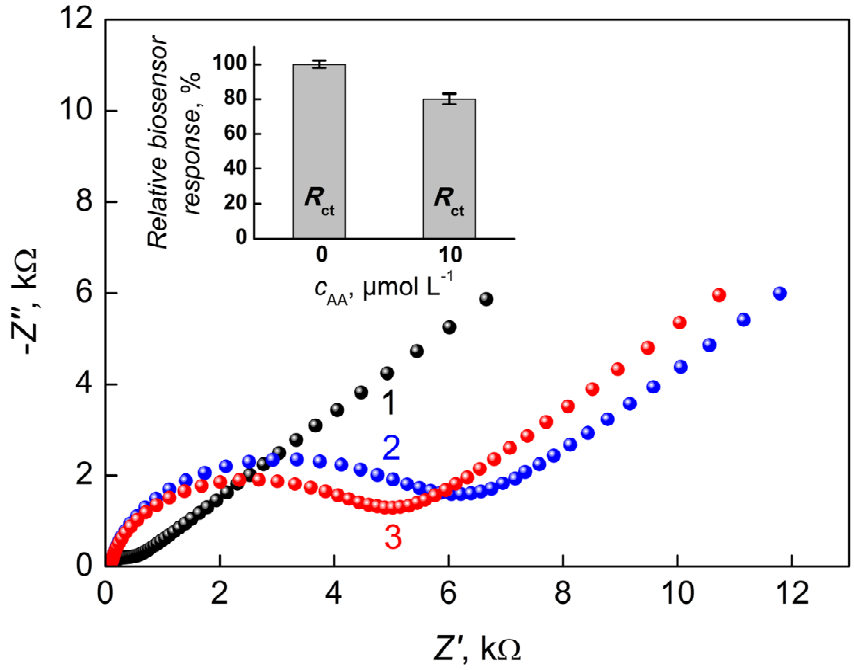

Fig. 2: *Nyquist plots in the presence of 1×10^{-3} mol L^{-1} $[Fe(CN)_6]^{4-/3-}$ in 0.1 mol L^{-1} phosphate buffer of pH 7.0* [59]. Legend: (**1**) measured at a bare GCE, (**2**) measured at a DNA-modified GCE after 5 min incubation of the biosensor in 0.1 mol L^{-1} phosphate buffer of pH 7.0, and (**3**) measured at a DNA-modified GCE after 5 min incubation of the biosensor in 0.1 mol L^{-1} phosphate buffer of pH 7.0 containing 1×10^{-5} mol L^{-1} 2-aminoanthracene (AA). Experimental conditions: polarization potential 0.21 V *vs.* Ag|AgCl, potential amplitude 0.01 V, frequency range 0.1 – 5000 Hz (51 frequency steps). Inset: the relative biosensor responses to DNA damage caused by AA, evaluated from the changes in the charge transfer resistance (R_{ct}) values; the error bars are constructed for the significance level of 0.05 (n = 3).

deep DNA degradation [54]. Decrease of the anodic guanine moiety peak height or area relative to that yielded by intact DNA was suggested as a measure representing degree of damage to this nucleobase and proposed as a screening test for environmental pollutants present in water or wastewater samples [9]. Some products of the DNA damage exhibit characteristic electrochemical signals (*e.g.*, anodic peaks of 8-oxo-7,8-dihydroguanine [60] and 2,8-dihydroxyadenine [61] moieties) which can be evaluated with better sensitivity than the change in original guanine moiety response.

The second group of techniques employs electroactive compounds added to the measured system and interacting with DNA non-covalently as its indicators (cationic indicators, intercalators and groove binders). Decrease in the intercalator or groove binder response indicates strand breaks and helix destruction.

The redox indicators may be also used as diffusionally free species present in the solution phase. For instance, the $[Fe(CN)_6]^{4-/3-}$ anions indicate the presence of DNA layer on the electrode surface on the basis of electrostatic repulsion between the indicator anion and negatively charged DNA backbone (Fig. 2) [62,63].

Moreover, investigated xenobiotic compound itself can serve as redox indicator. While its peak potential is shifted in the positive direction when the analyte binds to DNA by intercalation between the stacked base pairs of dsDNA, the peak potential is shifted in the negative direction when the interaction with DNA occurs by electrostatic attraction (interaction with the negatively charged nucleic sugar-phosphate structure) [64].

Investigated Organic Xenobiotic Compounds

There are thousands of organic compounds that bind and interact with DNA and can cause serious human diseases. The factors that determine affinity and selectivity in binding molecules to DNA need to be explained, because a quantitative understanding of the reasons that determine selection of DNA reaction sites is useful in designing sequence-specific DNA binding molecules for application in chemotherapy and in explaining the mechanism of action of genotoxic compounds [25].

DNA damage induced by environmental pollutants (a lot of them are marked as chemical carcinogens) (Table I) is a major endogenous toxicity pathway in biological system [65]. Most of organic pollutants may not directly cause DNA damage but their metabolized products by enzyme reactions are genotoxic and may cause the DNA lesion [24,66]. Electrochemical DNA biosensors enabling detection of such DNA damage could serve as a basis for *in vitro* genotoxicity screening for new organic chemicals at an early stage of their commercial development. For example, styrene is one of the most widely used industrial chemicals and itself shows little genotoxicity [67]. However, after being metabolized by liver cytochrome P450 enzymes, its oxidized product styrene oxide can induce DNA damage by formation of DNA adducts [68-70]; styrene oxide is classified by the International Agency for Research on Cancer (IARC) as a probable human carcinogen (group 2A) [71].

A number of aromatic compounds induce oxidative DNA damage through the generation of ROS. ROS produced *in vivo* react with DNA and its precursors modifying them thus giving rise to the so-called oxidative stress. It is thought that the modification of DNA (DNA lesions) leads to the formation of incorrect base pairs (changes in the genetic

information), which induces mutagenesis and carcinogenesis. Therefore, there is a deep interest in identifying free radical scavengers or antioxidants that inhibit oxidative DNA damage (Table I). Owing to their polyphenolic nature, flavonoids (compounds found in rich abundance in all land plants) often exhibit strong antioxidant properties [72-76]. Initially, flavonoids were investigated as potential chemopreventive agents against certain carcinogens. Previous intake of a large quantity of flavonoid inhibited the incidence of ROS produced damages to DNA. In sharp contrast with their commonly accepted role, there is also considerable evidence that flavonoids themselves are mutagenic and have DNA damaging ability [25,73,74].

In agriculture, farmers use numerous pesticides to protect crops and seeds before and after harvesting. Pesticide residues may enter into the food chain through air, water, and soil. They affect ecosystems and cause several health problems to animals and humans. Pesticides can be carcinogenic and cytotoxic. They can produce bone marrow and nerve disorders, infertility, and immunological and respiratory diseases [77]. Recently, an electrochemical DNA biosensor was developed to study DNA damage caused by several pesticides, such as atrazine, 2,4-dichlorophenoxyacetic acid (2,4-D), glufosinate ammonium, carbofuran, paraoxon-ethyl, and difluorobenzuron [78]. A biotinylated DNA probe was immobilized on a streptavidin-modified electrode surface. This DNA probe was hybridized with biotinylated complementary DNA target analyte. Streptavidin labeled with ferrocene was further attached to the hybridized biotinylated DNA. The close proximity of ferrocene to the electrode surface induced a current signal. The presence of pesticides caused an unwinding of the DNA and thus a decrease of the ferrocene oxidation current observed in voltammetric experiments. Paraoxon-ethyl and atrazine caused the fastest and most severe damage to DNA [78]. Some other papers dealing with investigation of interactions between individual pesticides and DNA are mentioned in Table I.

The interaction of DNA with drugs (Table I) is among the important aspects of biological studies in drug discovery and pharmaceutical development processes [79]. There are several types of interactions associated with drugs that bind to DNA. These include intercalation, non-covalent groove binding, covalent binding (formation of DNA adducts), DNA cleaving, or nucleoside-analog incorporation. Typical consequences of these binding interactions then involve changes to both the DNA and drug molecules to accommodate complex formation.

Table I: *A survey of compounds investigated using various electrochemical DNA biosensors in connection with DNA damage*. Selected papers published during the last five years (2008 – 2012).

Xenobiotic compound	Detection technique	Transducer	Type of damage	Ref.
Antioxidants				
Gallic acid	DPV	GCE	Intercalation	[80]
Hesperitin	DPV	GCE	Intercalation	[81]
Myricetin	CV	HMDE	No damage detected	[82]
Naringenin	DPV	GCE	Intercalation	[81]
Rutin	DPV	GCE	Intercalation	[83]
	CV, DPV	MWCNT/GCE	Adduct formation	[84]
Chemical carcinogens				
Acrylamide	DPV	Gp/PGrE	Adduct formation	[85]
Acrylonitrile	CV	PGrE	Oxidative damage	[86]
Aflatoxin B1	DPV	CPE	Intercalation	[87]
2-Aminoanthracene	SWV, EIS	GCE	Intercalation	[59]
Anthracene	SWV, EIS	GCE	Intercalation	[59]
2-Aminofluorene	CV, SWV	CFE	Intercalation	[88]
	SWV	SPCE	Intercalation	[89]
Benz[*a*]anthracene	CP	SPGrE	Intercalation	[90]
Benzene	CV, EIS	MWCNT/GCE	Intercalation	[91]
Bisphenol A	DPV	MWCNT/GCE	Intercalation	[92]
Catechol	DPV	GCE	Oxidative damage	[93]
2,7-Diaminofluorene	SWV	SPCE	Intercalation	[89]
2,7-Dinitrofluorene	CV, DPV, SWV	SPCE	Intercalation, oxidative damage	[24]
DMBA	DPV	PeGrE	Intercalation	[94]
Fluoren-9-one	SWV	SPCE	Intercalation	[89]
Glycidamide	DPV	Gp/PGrE	Adduct formation	[85]
Hydroquinone	DPV	GCE	Oxidative damage	[93]
Microcystin-LR	DPV	GCE	Aggregation of DNA strands	[95]
Nitrobenzene	DPV	HMDE	Intercalation	[96]
2-Nitrobiphenyl	DPV	HMDE	Intercalation	[96]
3-Nitrobiphenyl	DPV	HMDE	Intercalation	[96]
4-Nitrobiphenyl	DPV	HMDE	Intercalation	[96]
2-Nitrofluorene	CV, DPV, SWV	SPCE	Intercalation, oxidative damage	[24]
	CV, DPV	HMDE	Intercalation, oxidative damage	[97]
Nodularin	DPV	GCE	Aggregation of DNA strands	[95]

Table I: (*continued*)

Xenobiotic compound	Detection technique	Transducer	Type of damage	Ref.
Phenanthrene	CP	SPGrE	Intercalation	[90]
Proflavine	DPV	CPE	Intercalation	[98]
	ACV	HMDE	Intercalation	[98]
Styrene oxide	DPV, EIS	GCE	Adduct formation	[69]
	CV	PGrE	Adduct formation	[70]
Trichlorobenzenes	CV	GCE	Intercalation	[99]
		Drugs		
Amodiaquine	CV, DPV	CPE	Adduct formation	[100]
Amoxicilin	CV	MWCNT/GCE	Groove binding	[101]
Calcium dobesilate	CV, DPV	GCE	Intercalation	[102]
Carbamazepine	DPV	GCE	Intercalation	[103]
Daunorubicin	CV, DPV	GCE	Intercalation	[104]
Efavirenz	DPV	PeGrE	Intercalation	[105]
Ellipticine	SWV	HMDE	Intercalation	[106]
Epirubicin	CV	GCE	Intercalation	[107]
Flutamide	SWV, EIS	GCE	No damage detected	[59]
Gatifloxacin	DPV	GCE	Intercalation, electrostatic binding	[108]
	DPV	MWCNT-PE	Intercalation	[109]
Gemcitabine	DPV	GCE	Groove binding	[110]
Irinotecan	CV	HMDE	Electrostatic binding	[111]
Isoprenaline	CV, DPV	GCE	Intercalation	[112]
Kainic acid	DPV	GrE	Oxidative damage	[113]
Methotrexate	CV	GCE	Groove binding	[114]
	DPV	GCE	Intercalation	[115]
Mitomycin C	DPV, EIS	GpO/PeGrE	Adduct formation	[6]
Moxifloxacin	DPV	GCE	Intercalation, electrostatic binding	[108]
Nimodipine	CV, DPV	GCE	Electrostatic binding	[116]
Nitrofurantoin	CV, DPV	HMDE	Intercalation	[117]
Nitrofurazone	DPV	GCE	Electrostatic binding, oxidative damage	[23]
NTMA	SWV, EIS	GCE	No damage detected	[59]
Oncocalyxone A	DPV	GCE	Adduct formation	[118]
Prometazine	CV	AuE	Intercalation, electrostatic binding	[119]
Ractopamine	DPV	GCE	Intercalation	[120]
Sparfloxacin	DPV	GCE	Intercalation, electrostatic binding	[108]

Table I: (*continued*)

Xenobiotic compound	Detection technique	Transducer	Type of damage	Ref.
Taxol	CV, SWV	SWCNT/AuE	Intercalation	[121]
Thalidomide	DPV	GCE	Intercalation, oxidative damage	[122]
Thioridazine	CV, SWV, EIS	SWCNT/SPCE	Intercalation	[51,54]
Dyes				
Acridine orange	SWV	AuE	Intercalation	[123]
Calcein	CV	CCBPE	Intercalation	[124]
Nuclear fast red	CV, DPV	GCE	Groove binding	[125]
Purpurin	CV, DPV	GCE	Intercalation	[126]
Pesticides				
Carbofuran	DPV	GCE	Intercalation	[127]
2,4-D	ACV	HMDE	Groove binding	[128]
Fenitrothion	CV	HMDE	Intercalation	[129]
Other biologically active organic compounds				
Cobalamin	CV	GCE	Intercalation	[130]
Magnolol	LSV	GCE	Electrostatic binding	[131]
Menadione	CV	GCE	Intercalation, electrostatic binding	[132]
Nicotine	DPV	GCE	Electrostatic binding	[133]
2-Nitrophenol	DPV	GCE	Adduct formation, oxidative damage	[134]
4-Nitrophenol	DPV	HMDE	Adduct formation	[96]
4-Nonylphenol	DPV	Gp/GCE	Electrostatic binding	[135]
	DPV	SWCNT/PeGrE	Not determined	[136]
Riboflavin	DPV	PeGrE	Groove binding	[137]

Abbreviations used: ACV ... AC voltammetry, AuE ... gold electrode, CCBPE ... conductive carbon black paste electrode, CFE ... carbon film electrode, CP ... chronopotentiometry, CPE ... carbon paste electrode, CV ... cyclic voltammetry, 2,4-D ... 2,4-dichlorophenoxyacetic acid, DMBA ... 7,12-dimethylbenz[*a*]anthracene, DPV ... differential pulse voltammetry, EIS ... electrochemical impedance spectroscopy, GCE ... glassy carbon electrode, Gp ... graphene, GpO ... graphene oxide, GrE ... graphite electrode, HMDE ... hanging mercury drop electrode, LSV ... linear sweep voltammetry, MWCNT ... multi-walled carbon nanotubes, MWCNT-PE ... multi-walled carbon nanotubes paste electrode, NTMA ... 4-nitro-3-trifluoromethylaniline, PeGrE ... pencil graphite electrode, PGrE ... pyrolytic graphite electrode, SPCE ... screen-printed carbon electrode, SPGrE ... screen-printed graphite electrode, SWCNT ... single-walled carbon nanotubes, SWV ... square wave voltammetry.

In many cases, changes to the structure of the DNA duplex result in altered thermodynamic stability and are manifested as changes in the functional properties of the DNA [138].

Also specific fraction of organic dyes (acridine dyes, anthraquinone dyes, *etc.*) (Table I) belongs to the group of DNA intercalators (compounds able to interact with DNA through insertion of molecules with planar aromatic ring systems between DNA base pairs). For instance, acridine dyes have demonstrated to present mutagenic, carcinogenic, antibacterial, and antiviral properties [139]. Their similarity to several antibiotics, such as daunomycin or actinomycin, makes them interesting model systems for studying a variety of biophysicochemical problems [140]. Acridine derivatives initially bind (prior their intercalation between base pairs) to the minor groove of dsDNA through counter ion displacement [141,142].

Conclusions

In this contribution, it has been shown that the DNA-modified electrodes — alternately, electrochemical DNA biosensors — already represent very effective and, at the same, simple, fast, inexpensive, miniaturized, and mass-producible analytical devices for evaluation and classification of modes of genotoxic effects of the individual organic xenobiotic compounds (*e.g.*, chemical carcinogens, dyes, pesticides, or various industrial chemicals), as well as for pre-screening of new pharmaceuticals and drugs or various newly synthesized chemicals. Moreover, the evaluation of DNA protection capacity of various natural and synthetic chemical substances (antioxidants) is also possible using the detection of DNA damage caused by pro-oxidants.

It can be expected that, in a near future, complex biorecognition layers utilizing various supramolecular interactions will be suggested to detect potentially risk compounds and to improve further abilities of biosensors to detect damage to DNA. The advanced level of medical and clinical diagnosis will largely be dependent upon the successful development and implementation of new materials and technologies, thus envisaging the fabrication of state-of-the-art biosensors. Attractive properties of electrochemical devices are thus extremely promising for improving the efficiency of environmental screening, diagnostic testing, and therapy monitoring.

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