Nanosensors for Reactive Organophosphates

Subjects: Nanoscience & Nanotechnology

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Reactive organophosphates (OPs) comprise of collectively a group of phosphorous-based toxic chemicals that cause life-threatening toxic symptoms in humans. These include nerve agents and agricultural pesticides. Nanomaterial applications offer a high potential in developing nanosensors for sensitive OP detection and quantitative analysis.

Keywords: reactive organophosphate ; oxime ; nanomaterials ; sensors ; electrochemistry ; luminescence

1. Introduction

The term reactive organophosphates (OPs) refers collectively to a group of phosphorous-based toxic chemicals that cause life-threatening toxic symptoms in humans. These comprise OP nerve agents such as sarin, soman and VX, as well as OP-based pesticides like chlorpyrifos, paraoxon and malaoxon, among others (Figure 1) [1][2][3]. Despite their much lower toxicity, the OP pesticides are still formidable due to their wide distribution ranging from insect controls in the agricultural and horticultural sectors to pest treatments for domestic pets, farm animals and houses[4]. OP toxicity is commonly attributed to a phosphorous (thio)ester core that serves as its reactive functionality. It is highly susceptible to engaging in a covalent conjugation with a nucleophilic residue present in proteins and cellular enzymes in plasmas[1][5][6][7][8]. This OP reaction results in a covalent protein modification and thus loss of their original activity.
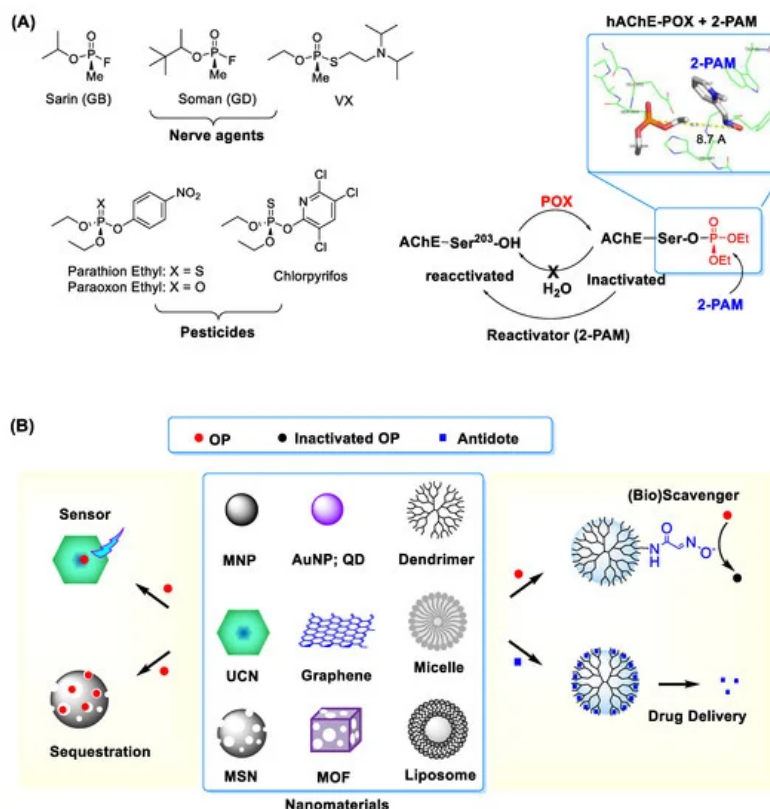

Figure 1. (**A**) (left) Types of representative organophosphates (OP) including nerve agents and pesticides and (right) covalent inhibition of acetylcholine esterase (AChE) by OP such as paraoxon ethyl (POX). Inset: An X-ray crystal structure for POX-inactivated human AChE in complex with 2-PAM, an enzyme reactivator which works by nucleophilic dephosphorylation (protein data bank (PDB) code 5HFA ref [9]). Adapted with permission from ref [10], Copyright 2019, The Royal Society of Chemistry. (**B**) Selected nanomaterials and their applications in OP detection and treatment. Abbreviations: MNP = magnetic nanoparticle, AuNP = gold (Au) NP, QD = quantum dot, MSN = mesoporous silica nanoparticle, MOF = metal-organic framework, UCN = upconversion nanocrystal.

OP exposures remain a source of serious safety concerns given the history of accidental or terrorist incidents and increasingly indiscriminate use of OP pesticides that is responsible for environmental pollution and crop contamination [11]. In particular, persistent exposures to OP pesticides result in delayed or chronic toxicity in affected organisms[2][3]. Despite such concerns, current capability to address OP issues remains suboptimal due to paucity of advanced technologies that enable for sensitive OP detection or effective treatment. Nanomaterials have made a growing impact on developing therapeutic agents [12][13][14][15][16][17][18][19] and sensors[20] in numerous areas. These are classified as a group of objects or structures in a nanometer size range which display functional properties distinct from bulk materials[21][22]. Such properties are characterized largely by their composition, size and shapes, which include nanospheres[23][24], nanotubes [25], planar nanosheets [26], nanodisks [26][27], nanocages [28] and nanorods [24] (Figure 1). They allow structural modifications and offer functional capabilities through magnetic control, light absorption, fluorescence, luminescence, cavity loading or pore gating. These properties make nanomaterials highly applicable for sensors[28], drug delivery platforms [12]or nanoscale reactors [29][30]. Therefore, nanomaterial applications offer a high potential to address existing OP-related serious problems.

2. Nanosensors for Reactive Organophosphate Detection

2.1. Electrochemistry

2.1.1. AChE-Immobilized Electrode

Electrochemical detection constitutes one of fundamental approaches in biosensor design for OP analysis [31]. This often relies on fabricating an OP-responsive electrode through its surface functionalization such as by immobilization with AChE [31][32][33][34]. This enzyme functionalization is therefore responsible for generating an OP-specific signal in amperometry or voltammetry when its immobilized enzyme loses its catalytic activity upon inactivation by OP [31][32][33]. This detection method is validated for its ability to detect individual OP pesticides or their mixture.

2.1.2. AChE-Immobilized Nanosensor

In an electrochemical nanosensor design, AChE is immobilized on the nanoparticle (NP) surface in lieu of the bulk electrode surface. This approach has been applied to magnetic nanoparticles (MNPs) such as iron oxide (Fe_3O_4) nanoparticle (IONP) [35] and nano Fe-Ni [36], each offering an important benefit of magnetic control. Thus, using AChE-immobilized MNPs allows temporal and spatial control of MNP localization in an working electrode or screen-printed electrode under an applied magnetic field [35] as reported by Rodrigues et al. In this study, they report unique benefits such as ability for nanosensor assembly on demand and convenience in electrode renewal (cleaning). These are otherwise not available simply by permanent AChE immobilization on the electrode surface. AChE immobilization in MNP-based nanosensors can be achieved by protein crosslinking through glutaraldehyde [35], Ni-histidine tag [37][38] or light responsive polymer [37]. Their sensitivity for OP detection is validated with pesticides such as chlorpyrifos and malathion with limit of detection (LOD) as low as sub nM (Table 1).

Table 1. Nanomaterial-enabled sensors developed for OP analysis.

Detection	Concept	Design	OP Analyte (LOD)
Electrochemistry	AChE Inhibition	IONP@AChE	Chlorpyrifos oxon, malathion (0.3 nM)
		nano Fe-Ni@AChE	Phosmet (0.1 nM)
		AuNP-CaCO$_3$@AChE	Malathion, chlorpyrifos (0.1 nM)
		nano Ag@Chitosan-AChE	POX (15 nM)
		MSN@AChE	Dimethoate (6.5 nM)
	Anti-OP Antibody	GNS@Anti-parathion Ab	Parathion (0.2 fM)
	OP Adsorption	rGO@Cu	Parathion, fenitrothion, malathion (3 nM)
		rGO@AuNP-polymer	Malathion (0.1 nM)
		GNS@AuNP	Parathion methyl (2 nM)
	OP Reaction	GO@AuNP-acetophenone oxime	Diethyl cyanophosphonate, dimethoate, fenitrothion

Detection	Concept	Design	OP Analyte (LOD)
Fluorescence (Luminescence) Spectroscopy	**AChE Inhibition**	**Cd-Te QD**	**Paraoxon, GB, VX (0.1–8.0 nM)**
	OP Adsorption	**CdTe QD**	**Chlorpyrifos (0.1 nM)**
		ZnS-Mn QD	**Diethyl phosphorothioate**
		Hf-doped MOF	**Methylphosphonate**
		AuNP@Rhodamine	**Ethoprophos (37 nM)**
	OP Reaction	**CdS QD + Eosin Y**	**Chlorpyrifos (29 nM)**
		UCN@Oxime probe	**Dimethoate (0.14 µM)**
Colorimetry & Spectrophotometry	**AChE Inhibition**	**AuNR + AChE**	**Dichlorvos (45 fM)**
	OP Adsorption	**AuNP, AgNP**	**Ethion, parathion**
		AuNP@Rhodamine	**Ethoprophos (37 nM)**
		Nano Ag@PVP	**Chlorpyrifos (14 nM)**

AuNP = gold nanoparticle; GNS = graphene nanosheet; rGO = reduced graphene oxide; IONP = iron oxide nanoparticle; MNP = magnetic nanoparticle; MOF = metal-organic framework; MSN = mesoporous silica nanoparticle; PVP = polyvinylpyrrolidone; QD = quantum dot; UCN = upconversion nanoparticle.

Non-magnetic NPs are also employed in developing electrochemical nanosensors. These include gold nanoparticle (AuNP) [39], nano Ag [40] and mesoporous silica nanoparticle (MSN) [41], each functionalized by AChE immobilization or non-covalent encapsulation for OP specificity. These nanosensors offer sufficient sensitivity to detect a wide range of OP pesticides as listed in Table 1.

2.1.3. Antibody-Immobilized Nanosensor

Another approach for OP detection involves using an antibody raised against a specific OP species. This is described in a study reported by Mehta et al. [42] in which an anti-parathion antibody was immobilized on the surface of graphene nanosheet (GNS). As a two-dimensional nanostructure, GNS displays an excellent degree of conductance for electrons, which is hence highly suited for application in electrochemical biosensing. This GNS-based immunosensor showed high detection sensitivity for parathion or parathion-like pesticides with LOD as low as fM [42]. However, despite such sensitivity, using an immunosensor has certain drawbacks because its employed antibody is able to recognize only a specific subset of OPs and not applicable to a broader spectrum of OPs [42].

2.1.4. OP-Responsive Nanosensor

As introduced briefly above, GNS display unique features in its structure and property beneficial for electrochemical OP detection. These include high surface area-to-volume ratio, ultralow thickness and high electronic conductance [43]. Their combination confers GNS with sensitive ability to respond to OP adsorption or reaction that occurs on its surface. This is illustrated with a copper-graphene nanocomposite in Figure 2A that shows ability to detect sulfur-containing OP pesticides [44]. Such GNS-based OP detection is further validated using copper-coated reduced graphene oxide (rGO) [44], AuNP-coated rGO [45] and AuNP-coated GNS [46]. Besides, GNS nanosensors are designed by surface modification with an OP-specific probe molecule that engages in selective OP recognition and/or its reaction. Huixiang et al. [47] validated this concept using GO@AuNP functionalized with 4-aminoacetophenone oxime. Thus, an electrode fabricated with this graphene nanocomposite has led to OP detection with LOD at low nM (Table 1).
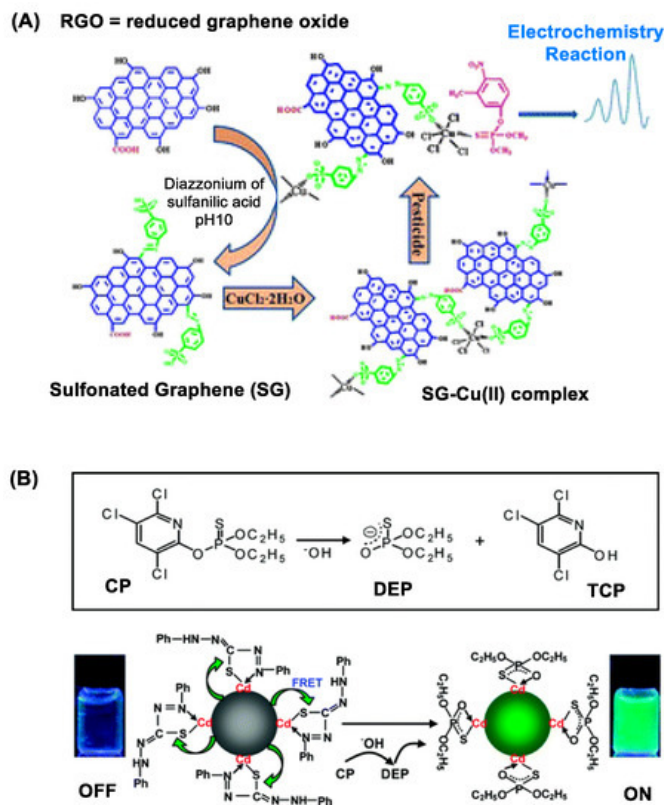
Figure 2. (**A**) A copper (II)-functionalized graphene nanocomposite applied for sensing sulfur-containing organophosphate (OP) pesticides. Reproduced with permission from [44], Copyright 2013, The Royal Society of Chemistry. (**B**) Dithizone-coordinated CdTe quantum dot (QD) applied for chlorpyrifos detection. Its concept of detection involves restoration of its fluorescence by dithizone replacement with diethylphosphorothioate, a hydrolytic byproduct of chlorpyrifos. Reproduced with permission from [48], Copyright 2010, American Chemical Society.

In summary, electrochemical nanosensors have shown promising capabilities for OP detection. These are designed with nanomaterials such as IONP [35][37][38], nano Fe-Ni [36], AuNP [39], nano Ag [40], MSN [41] or graphene-based NP [44][45][46][47], each functionalized with AChE [35][36][39][40][41], OP antibody [42] or OP-reactive moiety [47]. These nanosensors offer characteristic advantages including high loading capacity in electrodes, high sensitivity, and fast onset of action due to a narrow spacing between interacting electrodes. Their capabilities are attributable to a combination of their nanometer size, shape and other design features which are not available by conventional bulk electrodes [3][35].

2.2. Absorbance, Fluorescence and Luminescence Spectroscopy

In general, most OPs do not contain chromophores that are applicable for spectroscopic detection by UV–Vis absorbance or fluorescence. There are only few OPs which contain aromatic moieties for UV absorbance such as parathion, paraoxon (POX) and fenitrothion[49], each containing a 4-nitrophenyl group. However, their direct detection by spectrometry is not efficient because their molar absorptivity is practically too low for sensitive analysis. Instead, these are better detectable indirectly through a mechanism of fluorescence quenching in which each chromophore serves as a fluorescence quencher to a sensor molecule added separately such as coumarin [50]. This fluorescence quenching assay is validated with parathion, POX and fenitrothion, and it displays relatively low sensitivity in the range of 10^{-7}–10^{-4} M [49].

2.2.1. Quantum Dot (QD) Nanosensors

QDs are notable for their bright fluorescence in the visible and near infrared (NIR) range [48][51]. Their fluorescence is applicable for OP detection as illustrated with QD sensors made of CdTe [52][48], CdS [53] and Mn-doped ZnS [54]. Their detection principle varies with specific design features introduced in each sensor, but it involves measuring a change in QD fluorescence intensity that occurs in response to OP adsorption or a chemical reaction on the QD surface [52]. The change occurs via either fluorescence resonance energy transfer (FRET) [48][53] or photoelectron transfer (PET) [54] between the donor (QD) and the OP-responsive acceptor attached on the surface. Zhang et al. reported dithizone-coordinated CdTe QD designed for FRET quenching-based chlorpyrifos detection via dithizone hydrolysis as shown in Figure 2B [48].

2.2.2. Upconversion Nanocrystal (UCN) Nanosensors

UCNs belong in an emerging class of photoactive nanomaterials that include NaYF$_4$ doped with lanthanide ions (Yb, Er, Tm) in their lattice structure [55][56]. Unlike QDs, UCNs are excited by irradiation at longer NIR wavelengths (980 or 808 nm) with ability to emit upconversion luminescence at shorter visible wavelengths such as 475 nm [57]. Their luminescence intensity is sensitive to surface functionalization, and it can be quenched via its luminescence resonance energy transfer (LRET) to an acceptor molecule localized at a close proximity. In a recent study, Wang et al. [58] describes such luminescence quenching using UCN functionalized with an OP-reactive oxime probe on the surface (Figure 3A). This quenched luminescence is applicable for OP detection because it is restored when the oxime probe reacts with OP which leads to LRET deactivation. This UCN-based nanosensor has shown a detection sensitivity for diethyl chlorophosphate or dimethoate at μM [58].
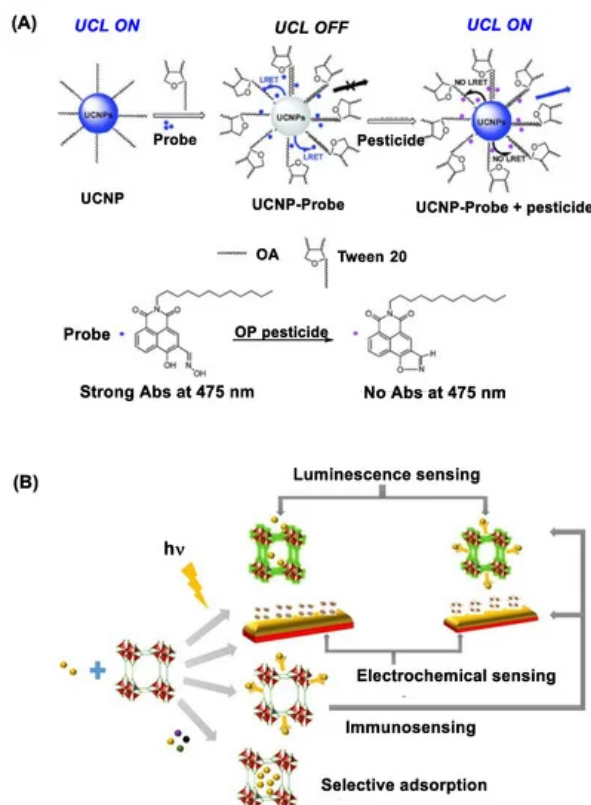

Figure 3. (**A**) Upconversion nanocrystal (UCN) immobilized with an oxime probe on the surface applied for OP detection through the mechanism of luminescence resonance energy transfer (LRET) between UCN and the oxime probe involved in organophosphate detection. Reproduced with permission from ref [58], Copyright 2016, The Royal Society of Chemistry. (**B**) A schematic diagram for metal-organic framework (MOF)-based approaches developed for pesticide sensing. Reproduced with permission from ref [59], Copyright 2018, American Chemical Society.

2.2.3. Metal-Organic Framework Nanosensors

OP can be detected by metal-organic frameworks (MOFs) that are active in UV photoluminescence. These include MOFs made of luminescent transition metal or lanthanide ions coordinated to organic ligands (imidazole) [60][61]. Their photoluminescence is highly responsive to microenvironmental changes in their lattice structure such as binding by guest molecules. Thus it is diminished to a significant extent upon OP binding or encapsulation (Figure 3B) [62]. This MOF-based luminescence assay enables to detect a broad spectrum of OP pesticides including chlorpyrifos, parathion and azinphos-methyl as described in a study by Singha et al. [63]. MOF sensors can be tunable in their design for improved guest specificity as reported with hafnium (Hf) ion-doped MOF [64]. In this study, Lian et al. describes its specific response to methanephosphonate, a hydrolytic byproduct from nerve agents, with high sensitivity. Other design factors in MOF sensors include those related to addressing potential drawbacks such as suboptimal aqueous stability, relatively slow onset of response and signal interference by other chemicals [59].

2.2.4. Plasmonic Nanomaterials

Noble metal nanomaterials that include nano gold (Au) or nano silver (Ag) display light absorbance via surface plasmon resonance (SPR) in the range of 350–500 nm (nano Ag) and 450–600 nm (nano Au)[24][65]. Their SPR absorbance is applicable for OP detection because it makes a blue shift upon chemisorption by sulfur analytes such as thiol-releasing OPs or thion (P=S)-based OPs (Table 1) [66]. Their detection sensitivity varies with metal compositions and shapes as evident with hexagon-shaped nano Ag which detects chlorpyrifos more effectively than other shapes [67].

Development of plasmonic nanosensors based on nano Au and nano Ag has certain limitations because they are not directly applicable for certain OPs that lack a sulfur moiety. Such lack of broader sensitivity is however addressed by surface functionalization with an OP-specific sensing element such as AChE [68], rhodamine B [69] or adenosine triphosphate [69]. Each of these sensors, which works in a different manner, has shown a broader sensitivity extended to oxon-based ethoprophos and dichlorvos [69][68] (Table 1).

In topic summary, several types of nanosensors are developed for OP analysis with improvement in detection time, sensitivity and specificity. Their capabilities are attributable to nanoscale structural and functional properties enabled by various types of nanomaterials that include MNPs [35][37][38], nano Au [39][69], nano Ag [40], MSN [41], graphene [42][44][45][46] [47], QDs[52][48][54], luminescent UCN [58] and MOF [64]. These nanosensors are applicable for instrumental OP analysis by electrochemistry, SPR absorbance, fluorescence and luminescence.

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