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18

Progress in Antidotes (Acetylcholinesterase Reactivators) Against Organophosphorus Pesticides

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1. Introduction

The use of pesticides allows human to stabilize and increase agricultural production (Wang 2009). Among various types of pesticides, the organophosphorus pesticides (OPP) are targeted to the insect elimination (Fukuto 1990). They were developed as esters of phosphonic or phosphoric acid or their thio-analogues e.g. paraoxon, chlorpyriphos, diazinon, dimethoate (Figure 1).

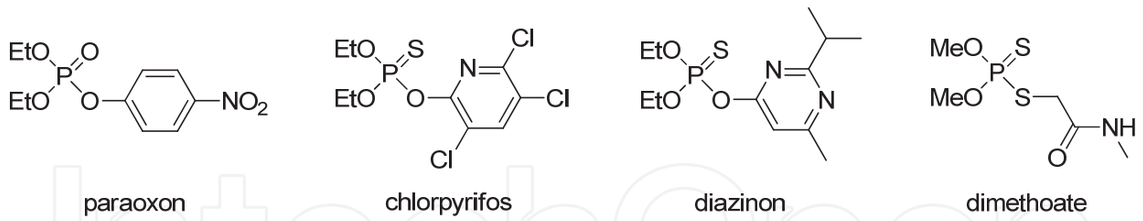


Fig. 1. Organophosphorus insecticides.

Their mechanism of action consists in the irreversible inhibition of cholinesterases in the insect body, namely acetylcholinesterase (AChE; EC 3.1.1.7) or butyrylcholinesterase (BChE; EC 3.1.1.8) (Marrs 1993). The cholinesterases irreversible inhibition is based on formation of covalent bond between OPP and serine moiety in the AChE active site. The AChE is responsible for termination of neuronal transmission via degradation of acetylcholine in the synaptic cleft. This irreversible AChE inhibition causes the accumulation of acetylcholine in the synaptic cleft and thus permanent activation of cholinergic (muscarinic or nicotinic) receptors (Bajgar 2004). The disrupted neuronal transmission causes the insect death (Brooks 1986).

However, the OPP are not selective for insect species, but they have same mechanism of action for the warm-blooded organism (Figure 2) including human (Bajgar 2004). Thus, the

human may be also easily intoxicated by OPP. Consequently, human AChE (hAChE) is irreversibly inhibited in Ser203 and cannot fulfil its natural function (Marrs 1993). The acetylcholine accumulation and consequent overstimulation of receptors leading to cholinergic crisis is common feature for such intoxication. The muscarinic (e.g. lacrimation, salivation, miosis), nicotinic (e.g. neuromuscular blockade) or central (e.g. breath depression) symptoms can be observed (Bajgar 2004). If the OPP intoxication remains untreated, the organism dies.

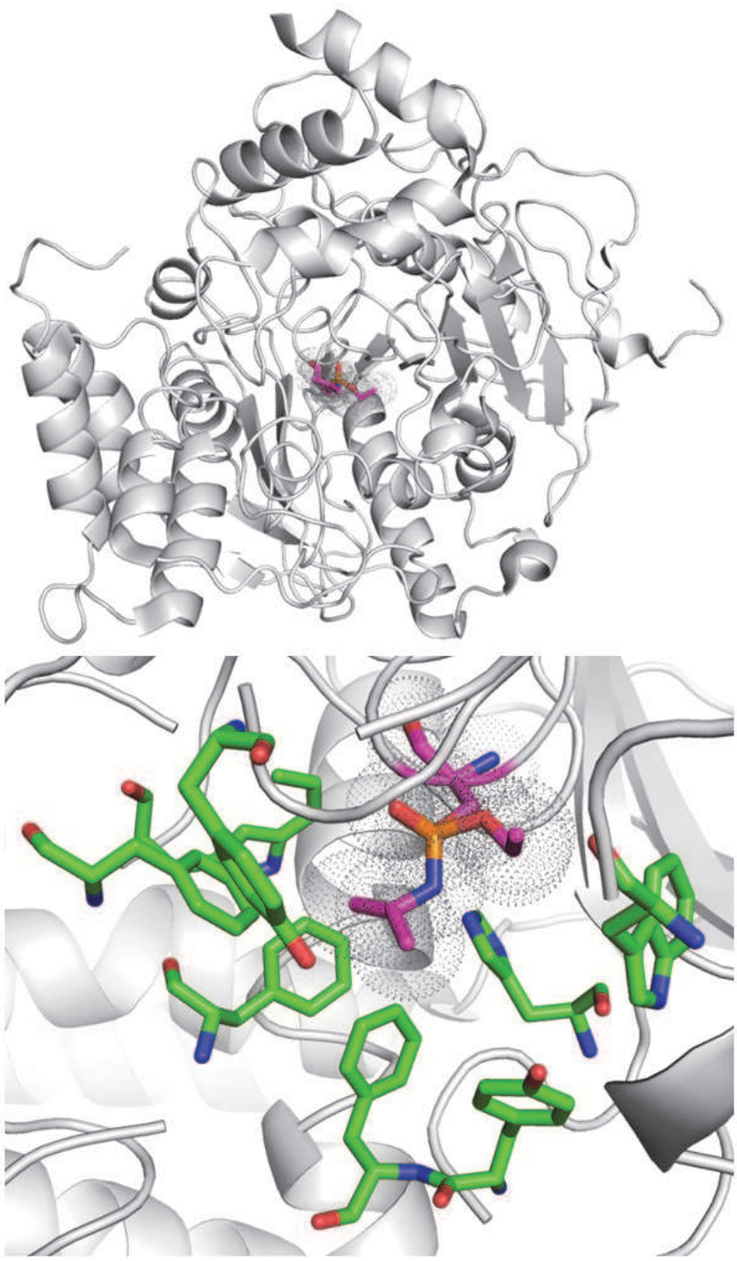


Fig. 2. Mice AChE inhibited by fenamiphos (in magenta; whole enzyme –left; active site – right; 2wu3.pdb) (Hornberg 2010).

The OPP intoxications of human are relatively widespread. They are usually arising from careless manipulation with OPP or the suicidal use of some OPP (Eddleston 2002). The terrorist misuse of the OPP should also not be underestimated from the point of view of food or water supplies contamination (Satoh 2000). The OPP intoxications were estimated to be annually responsible for 200 000 deaths that represent only about 15-30 % of all OPP intoxication (Eddleston 2008).

The general treatment of OPP intoxication has several necessary steps. The non-pharmacologic treatment is focused on resuscitation, oxygen supply or decontamination depending on the OPP entrance to the human body (e.g. skin, eye, gastric decontamination) (Eddleston 2008). The pharmacologic treatment consists in the administration of the symptomatic and causal drugs. The parasympatolytics (usually atropine; Figure 2) are used as the symptomatic treatment that is able to decrease the effects of the accumulated acetylcholine on the cholinergic receptors (Robenshtok 2002). Similarly, the anticonvulsives (usually diazepam; Figure 2) are used as the symptomatic treatment to decrease the neuromuscular seizures (Marrs 2003). Differently from symptomatic drugs, the AChE reactivators were developed as the causal treatment to cleave to OPP moiety from AChE serine active site and to reactivate its native function (Bajgar 2007).

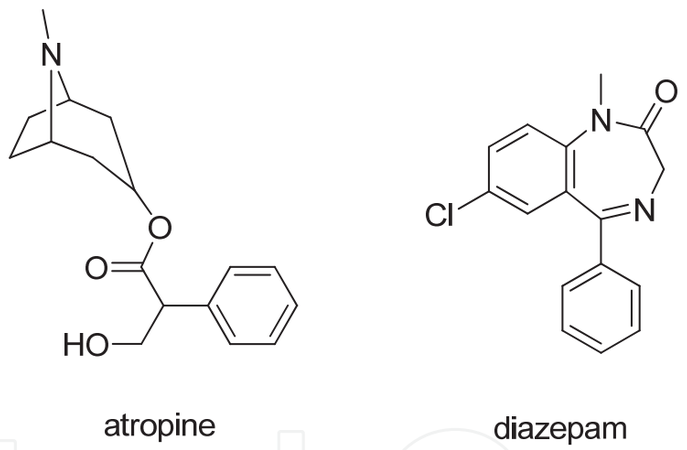


Fig. 3. Drugs used for symptomatic treatment of the OPP intoxication.

The mechanism of AChE reactivation consists in the nucleophilic attack of the reactivator towards the OPP moiety (Marrs 1993). This attack is provided by hydroxyiminomethyl (oxime) moiety. The covalent bond between OPP and AChE serine is cleaved, the complex of reactivator-OPP (phosphorylated reactivator) is formed and the AChE is reactivated (Figure 4) (Eyer 2003). If the reactivation is successful, the AChE function is fully restored. However, the "aging" process may also take place (Mason 1993). In this case, the OPP-AChE complex is degraded and further coordinated within the cholinesterase active site. Such "aged" OPP-AChE complex cannot be reactivated by known oxime reactivators (Worek 2007). The aging process is well known for highly toxic nerve agents (e.g. sarin, soman, tabun, VX), but it is also known for some OP insecticides (e.g. dimethoate, fenamiphos) (Hornberg 2010). For the aging reasons, the acute OPP intoxication should be rapidly treated by causal drugs (oxime reactivators) (Bajgar 2007).

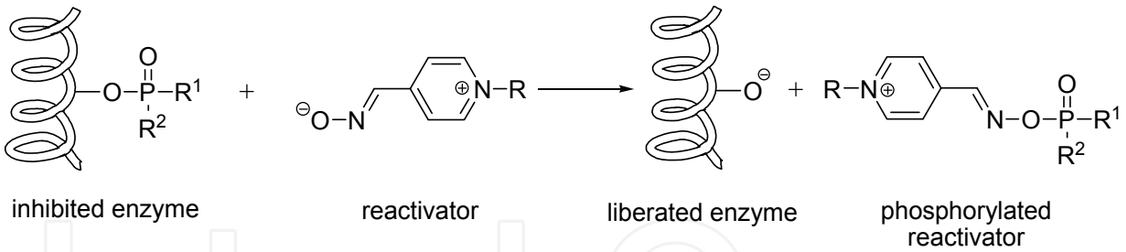


Fig. 4. Cholinesterase reactivation by oxime reactivator.

The oxime reactivators were developed since 1950´s. The original idea of cholinesterase reactivation came from reactivation activity of hydroxylamine analogues (Wilson 1953, Wilson 1955a-b). However, the better results were obtained from quaternary heteroaromatic compounds with oxime moiety. The pralidoxime (2-hydroxyiminomethyl-1-methylpyridinium chloride) was the first clinically used AChE reactivator (Figure 5) (Wilson 1955c, Namba 1958). Further, the bisquaternary compounds with one or two oxime moieties were developed – e.g. trimedoxime (1,1'-trimethylene-bis-(4-hydroxyiminomethylpyridinium) dichloride; Poziomek 1958), methoxime (1,1'-methylene-bis-(4-hydroxyiminomethylpyridinium) dichloride; Hobbiger 1960), obidoxime (1,1'-oxydimethylene-bis-(4-hydroxyiminomethylpyridinium) dichloride; Luettringhaus 1964), asoxime (HI-6; 1,1'-oxydimethylene-(2-hydroxyiminomethylpyridinium)-(4'-carbamoylpyridinium) dichloride; Hagedorn 1969; Figure 5).

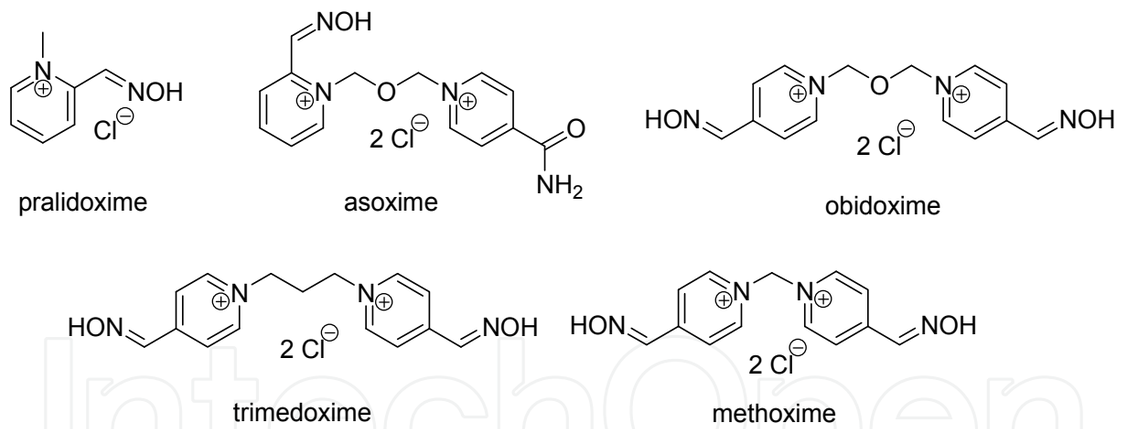


Fig. 5. Commercially available cholinesterase reactivators.

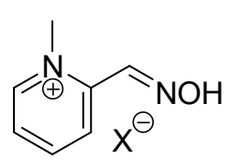
2. Commercially available acetylcholinesterase reactivators

The commercially available reactivators (pralidoxime, methoxime, trimedoxime, obidoxime, asoxime) were developed in the second half of the 20th century and more or less successfully used against intoxication by organophosphorus compounds. However, these reactivators were primarily aimed to diminish the intoxications by highly toxic nerve agents (Musilek 2011a). Thus, their use against OPP intoxications was usually made as a side process in the development of nerve agent antidotes. Though the commercially available reactivators were not directly pointed to OPP intoxication, some of them manifested satisfactory results in reactivation OPP inhibited cholinesterases.

2.1 Pralidoxime

The pralidoxime (Figure 6) was firstly described in 1955 and it was the first AChE reactivator available for clinical practice (Wilson 1955c, Namba 1958). Since 1950's, this drug was introduced globally and it remains in the standard treatment of OPP intoxication in many countries. However, the pralidoxime reactivation of OPP inhibited AChE was found to be debatable for many reason (Eddleston 2009). Whilst the reactivator concentration attainable in human blood after i.m. or i.v. administration was formerly suggested to be maximally 100 μM (Tattersall 1993), the *in vitro* studies reported limited pralidoxime reactivation of some OPP-inhibited (paraoxon, methylparaoxon, lephtophos-oxon, dichlorvos, methamidophos) hAChE (Table 1; Jun 2010, Jun 2011). Though pralidoxime presented some *in vitro* reactivation ability at 100 μM, it had limited reactivation at 10 μM that is more probably presented in human body after i.v. or i.m. administration of its suitable dose. Moreover, some published studies presented very high doses of pralidoxime *in vitro* (up to 700 μM), but did not consider attainable plasma concentration or possible adverse effects (Rios 2005). From *in vitro* evaluation point of view, pralidoxime seems not to be valuable reactivator for OPP intoxication compared to other commercially available compounds.

The *in vivo* animal studies concerned to pralidoxime also suggested its limited reactivation of OPP intoxicated animals. These findings were confirmed for e.g. paraoxon (Petroianu 2006a), methylparaoxon (Petroianu 2007a) or dichlorvos (Khan 1988). The pralidoxime was also determined with intermediate acute toxicity among standard five reactivators for mice and rats (Table 2; Musilek 2007a, Musilek 2010). Furthermore, many human studies with pralidoxime treatment of OPP intoxications are available, because pralidoxime chloride or dimethansulfonate is globally the most used cholinesterase reactivator and usually the antidote of the first choice. However, the pralidoxime was introduced to clinical practice without relevant clinical studies (Eddleston 2008). Thus, some randomised and double blind placebo controlled trials were made in the last two decades (Johnson 1996, Cherian 1997, Eddleston 2002). However, the opinion on pralidoxime effectiveness or ineffectiveness during OPP poisoning treatment had varied among such trials from the point of e.g. OPP type, OPP dose, delay before treatment, pralidoxime dosage (Buckley 2005, Eddleston 2008). Thus, the randomised controlled trial was performed (Eddleston 2009). Though patients with relatively low-dose occupational poisoning by diethyl OPPs showed clinically improvement after low-dose pralidoxime administration, the use of WHO recommended high pralidoxime doses did not improved survival of the OPP self-poisoned patients. Summarizing the *in vitro*, *in vivo* and human data, the use of pralidoxime remains questionable issue and it does not seem to be relevant drug of OPP poisoning treatment.



$X = Cl, CH_3SO_3$

pralidoxime

Fig. 6. Pralidoxime salts used against OPP intoxication.

	Reactivation±SD (%)									
Reactivator	**pralidoxime**		**methoxime**		**asoxime**		**trimedoxime**		**obidoxime**	
Reactivator concentration/ OPP (Reference)	100 μM	10 μM	100 μM	10 μM	100 μM	10 μM	100 μM	10 μM	100 μM	10 μM
paraoxon (Musilek 2011b)	10.7±0.3	2.1±0.1	16.1±0.5	1.8±0.3	6.2±0.6	1.7±0.1	44.3±0.6	22.5±1.3	59.7±1.0	22.4±0.4
methylparaoxon (Musilek 2011b)	30.2±0.3	22.4±0.7	14.2±0.1	14.3±0.2	13.6±0.2	17.9±0.4	51.4±0.9	59.5±0.7	61.7±0.3	45.3±0.9
leptophos-oxon (Jun 2010)	13.3±0.9	4.1±1.3	52.7±0.5	12.0±0.9	32.8±8.0	11.6±0.4	51.3±0.5	26.4±2.7	50.3±0.9	31.5±0
dichlorvos (Jun 2011)	2.6±0.6	0.2±0.6	0	0	0	0.6±1.1	0	0	2.0±1.2	3.3±2.3
methamidophos (Jun 2011)	53.4±3.1	53.8±22.6	61.7±2.4	68.1±11.4	37.4±12.3	75.2±14.6	9.4±7.5	53.1±10.9	45.0±0.5	93.5±3.9

Table 1. *In vitro* reactivation of human OPP inhibited AChE by commercially available oximes.

2.2 Methoxime and asoxime

The methoxime and lately asoxime (HI-6; Figure 7) were firstly described in 1960's (Hobbiger 1960, Hagedorn 1969). Both compounds were found to be very effective in case of nerve agent inhibited cholinesterases (Kassa 2002). Notably, the asoxime was found to be one of the most broad spectrum reactivators of nerve agent inhibited AChE up-to-date (Jokanovic 2008). However, asoxime was also found to be poor reactivator of dimethyl or diethyl OPP inhibited hAChE *in vitro*, if compared to other commercial reactivators (Table 1; Musilek 2011b, Jun 2010, Jun 2011). Similarly, the methoxime presented low reactivation ability for dimethyl or diethyl OPP inhibited hAChE, especially at human attainable concentration 10 μM. Thus, both compounds represent AChE reactivators with improved ability against nerve agents, but reduced for OPPs *in vitro*.

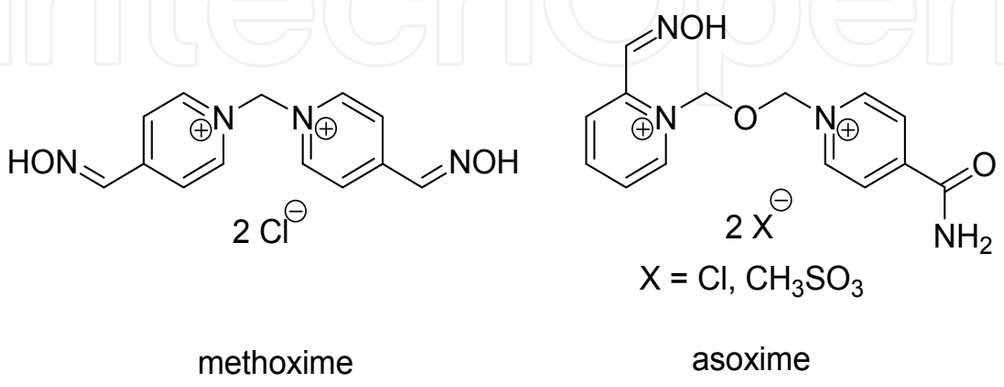


Fig. 7. Methoxime and asoxime salts available for organophosphorus intoxication treatment.

Reactivator/ Acute toxicity (Reference)	**pralidoxime**	**methoxime**	**asoxime**	**trimedoxime**	**obidoxime**
LD_{50} mice (mg/kg) (Musilek 2010)	263.6 (253.7-273.8)	641.8 (590.5-716.0)	671.3 (627.4-718.3)	149.3 (124.1–184.5)	188.4 (156.3–208.0)
LD_{50} rat (mg/kg) (Musilek 2007a)	377.5 (325.7-437.4)	441.8 (384.6-518.4)	781.3 (738.4-826.6)	150.5 (142.1-159.4)	211.07 (176.4-252.6)

Table 2. Acute toxicity of commercially available reactivators in mice and rat after i.m. administration.

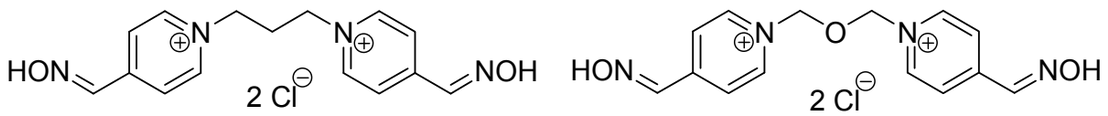
The *in vivo* animal data available for OPP reactivation by both compounds are very limited. Their acute toxicity for mice and rats was found very low among commercially available reactivators (Table 2; Musilek 2007a, Musilek 2010). The methoxime was suggested to be better AChE reactivator than pralidoxime for rats intoxicated by paraoxon (Petroianu 2006a). For methylparaoxon intoxicated rats, methoxime resulted as better reactivator than pralidoxime or obidoxime, but worse reactivator than trimedoxime (Petroianu 2007a). The asoxime use for *in vivo* animal model intoxicated by OPP was not found. Similarly, no relevant data of methoxime or asoxime use for human intoxicated by OPP were found. The explanation probably consists in poor *in vitro* reactivation of OPP by methoxime and asoxime that presumed their poor reactivation ability *in vivo* and the possible use of other potent reactivators. Though both compounds were found less toxic in comparison with other standard reactivators, they do not seem to be relevant drugs for OPP poisoning treatment, when only *in vitro*, limited *in vivo* animal data and no human data are available.

2.3 Trimedoxime and obidoxime

Trimedoxime and obidoxime were developed as bisquaternary bis-oximes with the aim to improve reactivation ability of pralidoxime (Poziomek 1958, Luettringhaus 1964). Both of them were successfully used against nerve agent inhibited AChE and belong to standards on the field (Antonijevic 2007). Their reactivation ability against OPP inhibited hAChE *in vitro* was found quite similar with slightly better results in case of the obidoxime. They were able to effectively reverse the dimethyl or diethyl OPP exposure *in vitro* at human attainable concentration 10 μM (Table 1; Musilek 2011b, Jun 2010, Jun 2011). Though their reactivation ability for dichlorvos inhibited hAChE remained poor, they resulted as the best hAChE reactivators of OPPs among five commercial standards *in vitro*.

The *in vivo* animal toxicity for rat and mice (Table 2; Musilek 2007a, Musilek 2010) assumes both trimedoxime and obidoxime as relatively toxic compounds among standard five oximes, when trimedoxime is the most toxic one. Plausibly, these finding may explain trimedoxime underutilization during OPP-animal studies, where relevant literature data were not found (Lorke 2009). On the other hand, the less toxic obidoxime was several times used for animals exposed to OPPs. The *in vivo* efficacy of obidoxime in rats exposed to paraoxon was found superior to pralidoxime (Nurulain 2009). The older study in parathion poisoned dogs suggested that obidoxime is able to reverse parathion inhibited AChE in blood and some brain areas (Kewitz 1980).

The human data for OPP poisoned patients with trimedoxime treatment are again not known. However, one study suggested that unintentional application of trimedoxime and



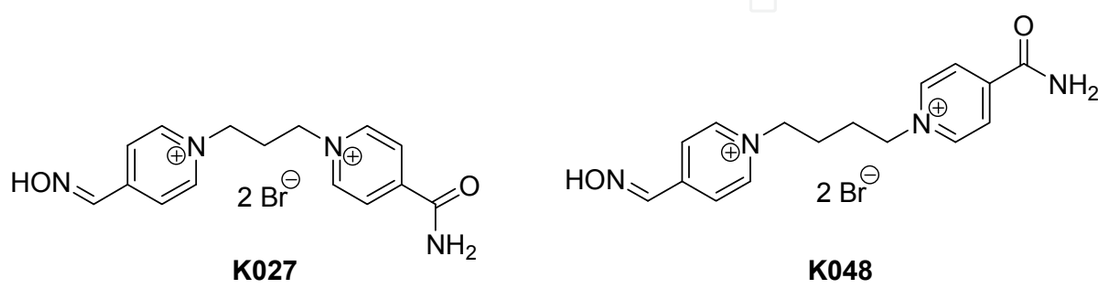
trimedoxime obidoxime

Fig. 8. Trimedoxime and obidoxime.

atropine combination from auto-injector to healthy adults causes only very mild adverse effects (Bentur 2006). More interestingly, similar study determined unintentional application of trimedoxime-atropine auto-injector to children in adult relevant doses, where no adverse effects related to trimedoxime were found (Kozer 2005). Both findings presume the safe human use of trimedoxime in human relevant doses. The obidoxime treatment of OPP poisoned patients was better reported. The combined obidoxime-atropine treatment was effective in patients poisoned by smaller doses of parathion, while the poisoning by the high dose of parathion was not successfully reactivated until parathion levels declined (Thiermann 1997). In the same study, obidoxime was reported as ineffective for oxydemetonmethyl poisoning, but the time elapsed between ingestion and oxime therapy was longer than one day (Thiermann 1997). The enzyme-based assay for quantification of paraoxon in blood of parathion poisoned patients confirmed significant obidoxime reactivation of low plasma paraoxon concentration, whilst diethylphosphoryloxime formation during obidoxime-induced reactivation did not markedly contribute to the re-inhibition of AChE (Eyer 1998). Though obidoxime presented some increased animal toxicity, it seems to be convenient oxime for treatment of human OPP poisoning from the standard five AChE reactivators in human relevant doses.

3. Upcoming acetylcholinesterase reactivators

There were many attempts to develop potent AChE reactivators for treatment of OPP poisoning (Musilek 2011a). Besides the oximes developed against nerve agents (Musilek 2007b), there were over 300 oximes prepared and tested. In the last decade, some of them presented very promising results against OPP exposure. Namely, some mono-oximes from K-compound series such as K027 (1,1'-trimethylene-(4-hydroxyiminomethylpyridinium)-(4-carbamoylpyridinium) dibromide; Kuca 2003a; Figure9) and K048 (1,1'-tetramethylene-(4-hydroxyiminomethylpyridinium)-(4-carbamoylpyridinium) dibromide; Kuca 2003b; Figure 9) were highlighted against some OPP poisoning *in vitro* and *in vivo*.



K027 **K048**

Fig. 9. Novel AChE reactivators developed for treatment of OPP poisoning.

Both compounds showed some reactivation of dimethyl- and diethyl-phosphorylated human AChE *in vitro* (Table 3; Musilek 2011b). The oxime K027 resulted better than K048 at both used concentration for paraoxon inhibited hAChE and almost comparable with the best commercial oxime against OPP (obidoxime) at human attainable concentration 10 μM. On the other hand, obidoxime was found superior to K027 or K048 for methylparaoxon inhibited hAChE *in vitro*. Though the obidoxime was again superior to K027 or K048 for leptophos-oxon inhibited hAChE at human attainable concentration 10 μM, the results of obidoxime and K027 reactivation at higher concentration (100 μM) were found quite similar.

	Reactivation±SD (%)					
Reactivator	**K027**		**K048**		**obidoxime**	
Reactivator concentration/OPP (Reference)	100 μM	10 μM	100 μM	10 μM	100 μM	10 μM
paraoxon (Musilek 2011b)	48.0±0.5	20.8±1.0	25.7±0.7	12.5±0.2	59.7±1.0	22.4±0.4
methylparaoxon (Musilek 2011b)	55.6±0.7	33.9±0.3	54.4±0.9	29.1±0.4	61.7±0.3	45.3±0.9
leptophos-oxon (Jun 2010)	49.3±0.5	16.4±0.9	26.1±0.4	6.6±0.4	50.3±0.9	31.5±0

Table 3. *In vitro* reactivation of human OPP inhibited AChE by promising upcoming oximes.

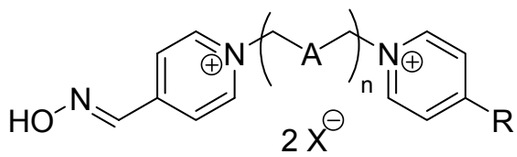
The *in vivo* animal data of K027 and K048 showed some interesting findings. Firstly, their acute toxicity was found lower than toxicity of trimedoxime or obidoxime in mice and rats (Table 4; Calic 2006, Lorke 2008, Kovarik 2009, Musilek 2010). Whereas reactivator K048 was only slightly less toxic than obidoxime, compound K027 was found to be less or comparable toxic with methoxime or asoxime that are the least toxic commercial reactivators (Table 2). The low acute toxicity of K027 might allow its higher dosage in comparison with obidoxime. Secondly, the experiments with rats exposed to paraoxon and methylparaoxon showed that both K027 and K048 provided statistically significant protection against chosen OPPs *in vivo* (Petroianu 2007a-b). Unfortunately, there are no available data for other animal species (e.g. guinea-pigs, pigs, dogs, monkeys) that might confirm/disprove published findings and predict reactivation effect of K027 or K048 in human (Worek 2011). Nevertheless, oxime K027 presented up-to-date very promising results in reactivation of some OPPs that are comparable or better than the best commercially available compound (obidoxime) together with K027 decreased animal toxicity. For these reasons, further experiments are necessary and might reveal K027 valuable properties in reactivation of OPP inhibited AChE.

Reactivator/Acute toxicity (Reference)	**K027**	**K048**	**Obidoxime**
LD_{50} mice (mg/kg) (Calic 2006, Musilek 2010)	672.8 (599.0–755.3) i.p.	224.9 (154.2–328.0) i.p.	188.4 (156.3–208.0) i.m.
LD_{50} rat (mg/kg) (Musilek 2007a, Lorke 2008, Kovarik 2009)	612.0 i.p.	238.3 (199.7-284.3) i.p.	211.07 (176.4-252.6) i.m.

Table 4. Acute toxicity of promising upcoming reactivators in mice and rat.

4. Structure activity relationship of AChE reactivators for OPP intoxication

From the point of view of medicinal chemistry, some trends based on structure activity relationship (SAR) may be considered for reactivators of OPP inhibited AChE (Figure 10; Musilek 2011a). Concerning the functional group, the oxime moiety remains essential for the activity of the reactivator (Kuca 2006). Its position on the heteroaromatic ring influences the reactivation ability. The 4-position of oxime moiety is preferred for OPPs reactivation,



A: $(CH_2)_{3\text{-}4}$; CH_2OCH_2; ???
R: CH=NOH; $CONH_2$; ???

Fig. 10. Structural model suitable for reactivation of OPP inhibited AChE.

instead of the 2-position or 3-position (De Jong 1981). This finding is affected by pKa, where the 3-positioned oxime has a high value, and also by steric hindrance of the reactivator molecule (Cabal 1998). The increased quantity of the oxime moieties in the molecule of AChE reactivator is not essential for reactivation and it usually increases toxicity (Musilek 2007a). The mono-oxime compounds (K027, K048) showed similar or higher reactivation ability compared to bis-oximes (trimedoxime, obidoxime) and presented a lower animal toxicity (Lorke 2009).

Additionally, bisquaternary compounds were found to be superior to monoquaternary compounds (Kuca 2006). Apparently, cation-π or π-π interactions with AChE aromatic residues (His, Phe, Trp, Tyr) are responsible for these findings (Musilek 2010, Musilek 2011b). Among various used heteroaromatic moieties, the pyridinium compounds were the most often utilized. Other moieties (e.g. 5-membered rings) did not show satisfactory reactivation which might be caused by inappropriate pKa values or steric hindrance within the enzyme active site (Cabal 1998).

Concerning the connecting linker at bisquaternary compounds, it has a significant effect on reactivation capability and toxicity. The length and constitution of the linker are the most important factors. For OPPs, alkylene linkage from 3 to 5 equivalents of C-C bond was found to be optimal for reactivation (Kuca 2003a-b), whereas the animal toxicity was not affected by this type of linkage (Petroianu 2006b). The addition of a double bond or an aromatic moiety (source of π-electrons) increased the reactivation ability, but it also increased reactivator toxicity (Musilek 2005, Musilek 2006, Musilek 2007c-e, Musilek 2010).

Concerning the non-oxime part of the molecule, various functional groups may be introduced to increase the reactivation ability as was found beneficially with the use of 3- or 4-carbamoyl, methylcarbonyl or isoquinolinium moieties (Musilek 2007a, Musilek 2007e, Musilek 2008). Indeed from a toxicity point of view, the carbamoyl, carboxyl and methylcarbonyl moieties were found to be very promising candidates (Kassa 2008, Kassa 2009, Berend 2008).

5. Conclusion

The organophosphorus pesticides (OPPs) are heterogeneous group of organophosphorus compounds. Their biological activity manifests as inhibition of cholinesterases and so ranks them as life endangering agents. The necessary treatment of OPP exposure contains parasympatholytics (e.g. atropine), oxime reactivator and anticonvulsive drug (e.g. diazepam) (Bajgar 2007). The causal treatment of organophosphorus intoxication (oxime reactivator) varies globally among five commercial compounds. Recently, the most important oximes in case of OPP intoxication are pralidoxime and obidoxime. Although

pralidoxime was the first oxime available for OPP treatment and it is currently the most frequently used, its ability to reactivate AChE inhibited by various OPPs, is rather poor (Buckley 2011). Consequently, bisquaternary compounds have been found to be more effective. Surprisingly, asoxime developed for nerve agent intoxication, showed in the case of OPPs intoxication, little or no reactivation capability (Stojiljkovic 2006). On the other hand, the trimedoxime and obidoxime were found to be very good for the treatment of OPP intoxication. Specifically, obidoxime should be the first choice compound in combination with atropine and diazepam for a positive clinical outcome (Stojiljkovic 2006).

Since the first use of pralidoxime against OPP intoxication, over 300 different oximes have been synthesized and evaluated (Musilek 2011a). From these, there are some very promising novel reactivators produced in the last decade. Though some of them were originally developed for nerve agent poisoning, they showed increased reactivation ability against various types of OPPs. Notably, compound K027 showed an increased reactivation capability (dimethoxy- and diethoxy- OPPs) with decreased toxicity, as compared to commercial compounds both using *in vitro* and *in vivo* animal models (Petroianu 2006a-b, Petroianu 2007a-c). These findings make compound K027 the lead compound for further studies and development.

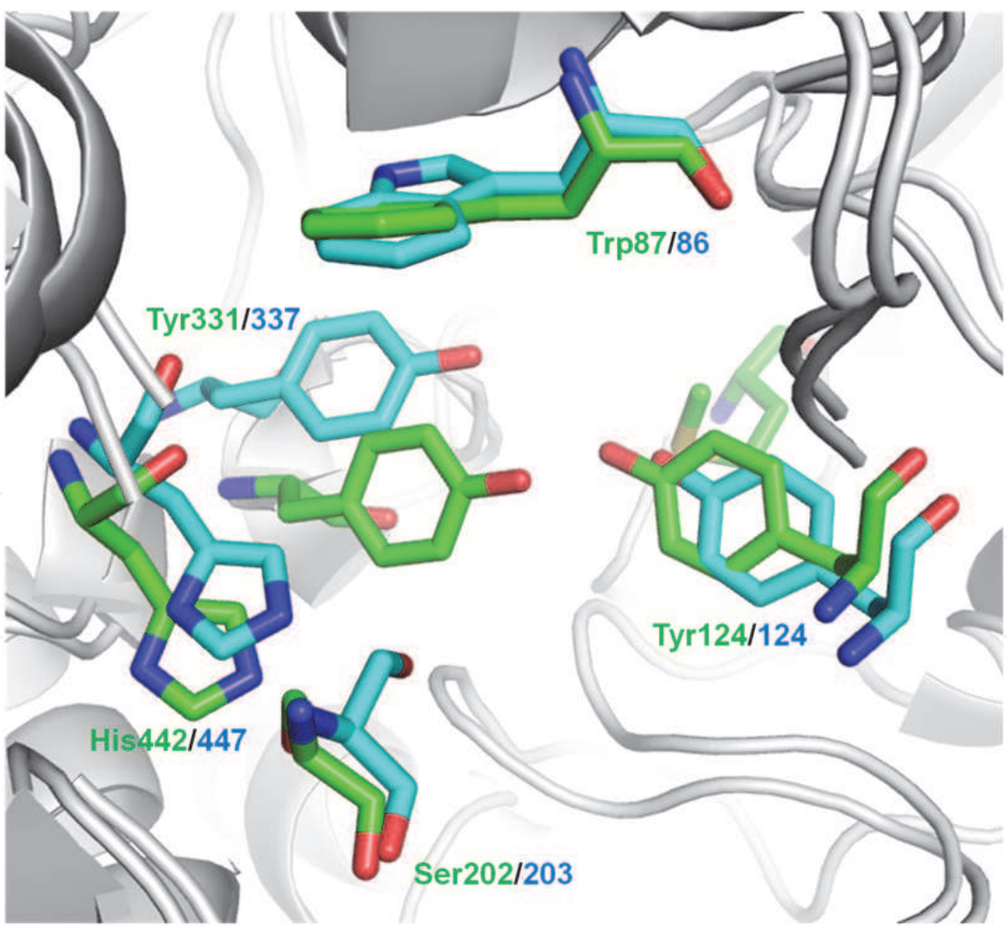


Fig. 11. Structural differences between aphid/human AChE (green/blue; 2hcp/1b41.pdb) AChE (Kryger 2000, Pang 2007).

Additionally, molecular modelling has become an important technique for understanding the mechanisms of OPP action in the last decade. Namely, OPP inhibit the AChE active site differently than the nerve agents. This experience will most probably be used for the future design of new antidotal compounds. Additionally, safer OPPs more specific for insect parasites may be constructed based on the differences between insect and human AChE (Figure 11; Pang 2009a-b).

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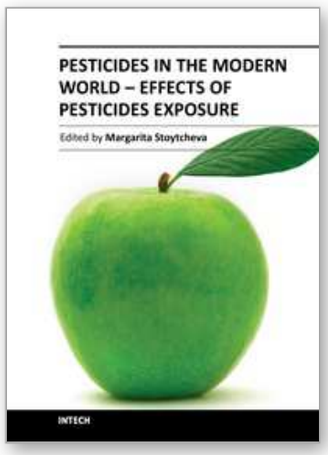

Pesticides in the Modern World - Effects of Pesticides Exposure

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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950â€™s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestockâ€™s yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising worldâ€™s population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

How to reference

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