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COMPARISON OF THE MECHANISMS OF ACTION OF SARIN AND OTHER ORGANOPHOSPHORUS INHIBITORS

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Abstract
This article provides a comparative analysis of the mechanisms of action of sarin and other organophosphorus inhibitors belonging to the group of highly toxic nerve agents. It focuses on the biochemical and molecular features of the interaction of these compounds with acetylcholinesterase, including the processes of phosphorylation of the enzyme's active site, the rate and reversibility of inhibition, and the influence of structural differences between the molecules on their toxicokinetics and toxicodynamics. The factors determining the degree of "aging" of the phosphorylated enzyme, the potential for acetylcholinesterase reactivation by oximes, and the effectiveness of antidote therapy are discussed. A comparative analysis of sarin, soman, and VX is provided in terms of their chemical properties, lethality, stability, and rate of penetration into the body. The results of this study provide a deeper understanding of the principles of action of nerve agents and potential approaches to the development of effective protective measures and treatments for exposure to them.

Keywords: Organophosphorus inhibitors, acetylcholinesterase, mechanisms of action, toxicity, effects on the body, treatment.

Relevance of the work

The relevance of studying the mechanisms of action of organophosphorus inhibitors of acetylcholinesterase (OP AChE inhibitors), their comparative analysis, and assessment of health effects is determined by the high toxicity of

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these compounds, their widespread domestic and agricultural use, their potential military–toxicological application, and the need for an in-depth understanding of the molecular processes underlying their biological activity [5]. OP inhibitors irreversibly disrupt the functioning of acetylcholinesterase, leading to the accumulation of acetylcholine, the development of severe cholinergic syndrome, and damage to the central and peripheral nervous systems. This underscores the importance of investigating inhibition kinetics, the "aging" processes of the enzyme–inhibitor complex, and the differences among individual classes of organophosphorus compounds [5]. Comparison of the structural features and toxicodynamics of various OP inhibitors is necessary to predict their hazard, refine diagnostic criteria, select optimal therapeutic strategies, and develop new antidotes. Considerable attention is also directed toward the long-term consequences of exposure, including cognitive impairment, neuroinflammation, metabolic disturbances, and chronic neurological effects. In addition, the study of OP inhibitors has practical significance for improving rapid diagnostic methods, preventing occupational risks, regulating pesticide use, conducting environmental monitoring, and enhancing global chemical safety. Thus, investigation of the mechanisms of action of organophosphorus AChE inhibitors represents a complex interdisciplinary task essential for medicine, toxicology, industrial safety, and public health.

Aim of the study.

The aim of the study may consist in evaluating and comparing the features of the mechanisms of action of various organophosphorus inhibitors at the molecular and physiological levels, identifying key similarities and differences that influence their toxicity, biological activity, and clinical consequences of exposure.

Introduction

Organophosphorus compounds (OPCs) were first synthesized by Thénard in 1846. [1] In Russia, the founder of OPC chemistry was A. E. Arbuzov, who in 1905 proposed a new method for their synthesis. Attention to the toxic properties

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of these compounds was drawn only in 1932, when Lange and Krüger first described symptoms of poisoning with dimethyl and diethyl fluorophosphate synthesized during the search for new insecticides. The undeniable practical significance of such agents led to large-scale studies aimed at a comprehensive investigation of this new class of biologically active substances. Thus, within a short period of time, more than 2,000 OPCs were synthesized and studied in Germany alone, in Schrader's laboratory, in the course of developing new means to control insect pests; many of these compounds exhibited high toxicity to mammals. This prompted the creation of new chemical warfare agents based on these substances. By the beginning of World War II, German chemists had synthesized such highly toxic agents as tabun and sarin, and somewhat later, soman. At the same time, prospects for the development of compounds even more toxic to humans were identified, which was realized in practice by Tammelin (1955), who synthesized methylphosphonofluoridate choline, serving as a prototype for a new group of nerve agents known as V-agents (VX). In the 1970s–1980s of the twentieth century, technologies for the use of nerve agents in so-called binary munitions were developed. In this approach, two relatively low-toxicity chemical components are stored, transported, and loaded into munitions separately; mixing occurs only after firing, forming a highly toxic organic compound en route to the target via a chemical reaction. The extremely high toxicity and physicochemical properties enabling rapid formation of extensive chemical contamination zones made nerve agents (sarin, soman, V-agents) among the most dangerous organic compounds known until recently [1]. In accordance with international agreements, stockpiles of nerve agents in most countries are subject to destruction.

When considering their chemical structure, they can be described as [4] organophosphorus compounds (OPCs)—organic compounds in which a phosphorus atom is bonded to a carbon atom either directly or through a heteroatom such as oxygen (O), sulfur (S), or nitrogen (N). OPCs are derivatives of pentavalent phosphorus acids. All toxic compounds of phosphoric (1), alkylphosphonic (2), and dialkylphosphinic (3) acids have the following general structure:

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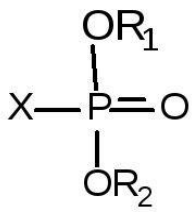
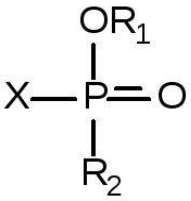


(1)



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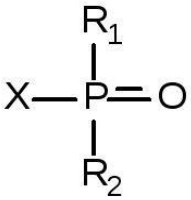
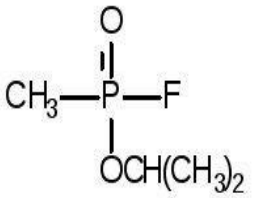
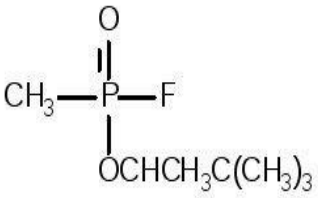


(3)

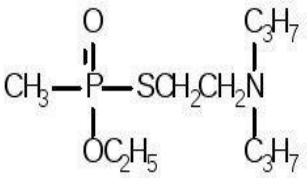
Phosphorus is bonded via a double bond to an oxygen or sulfur atom; through two single bonds it is connected to alkyl, alkoxy, aryl, mono- or dialkylamino groups, among others (R^1, R^2). The fifth substituent (X) is represented by a group that is relatively easily cleaved from the phosphorus atom (F^-, CN^-, –OR, –SR, etc.). As a result of the valence released during this cleavage, organophosphorus compounds are able to interact with the active sites of a number of enzymes. Representatives of this group of organic compounds can be depicted in the form of structural formulas as follows:



Sarin



Soman



VX

Before examining the interaction of the listed compounds with acetylcholinesterase, it is necessary to consider the non-pathological course of neurotransmission in the absence of organophosphorus compounds (OPCs) [4].

Role of acetylcholinesterase and the principle of inhibition

The membrane of one neuron that contacts another cell (a muscle cell or another neuron) forms a functional connection between excitable cells known as a synapse. Within the synapse, the presynaptic part—the axon terminal of the first cell, the synaptic cleft—the intercellular space separating the membranes of the contacting cells, and the postsynaptic part—a region of the second cell—are distinguished.

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In humans and warm-blooded animals, five neurotransmitters are known (including adrenaline). When neurotransmitters are inactive, they are stored in vesicles (synaptic vesicles) that isolate them from the intracellular environment. When a nerve impulse reaches the presynaptic terminal, depolarization of the terminal membrane occurs, increasing its permeability to calcium ions. The influx of calcium ions into the presynaptic region triggers the release of the neurotransmitter: the vesicle fuses with the membrane, and acetylcholine, which possesses high chemical reactivity, is released into the synaptic cleft and subsequently reaches the postsynaptic membrane of the target cell, thereby inducing the generation of an electrical potential [3]. The role of the enzyme acetylcholinesterase is to terminate excitation by hydrolyzing acetylcholine. This entire process occurs within fractions of a second (milliseconds). In the absence of acetylcholinesterase, or when the enzyme is blocked by a pesticide, free acetylcholine accumulates in the synaptic cleft, resulting in disruption of normal nerve impulse transmission. This leads to tremor (convulsive muscle activity), which can progress to paralysis [3].

Mechanism of action of sarin Sarin (GB, O-isopropyl methylphosphonofluoridate) is a highly toxic organophosphorus compound whose primary mechanism of action is based on irreversible phosphorylation of the active site of acetylcholinesterase (AChE). Inhibition of the enzyme results in pathological accumulation of acetylcholine (ACh) in cholinergic synapses. As a consequence, normal nerve impulse transmission is disrupted, leading to pronounced cholinergic hyperstimulation[2].

In the central nervous system (CNS), an excess of acetylcholine (ACh) induces seizure activity, neuronal hyperexcitability, and depression of the respiratory centers, thereby contributing to the development of fatal respiratory failure. In the peripheral nervous system, excessive stimulation of muscarinic and nicotinic receptors leads to manifestations of a cholinergic crisis (miosis, bronchospasm, hypersecretion, and gastrointestinal motility disorders) and may be accompanied by paralysis of the respiratory musculature as a result of acetylcholine overload at neuromuscular synapses [2].

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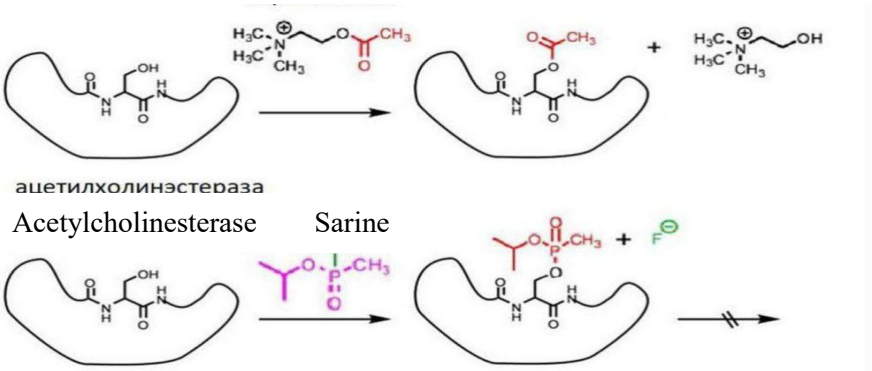
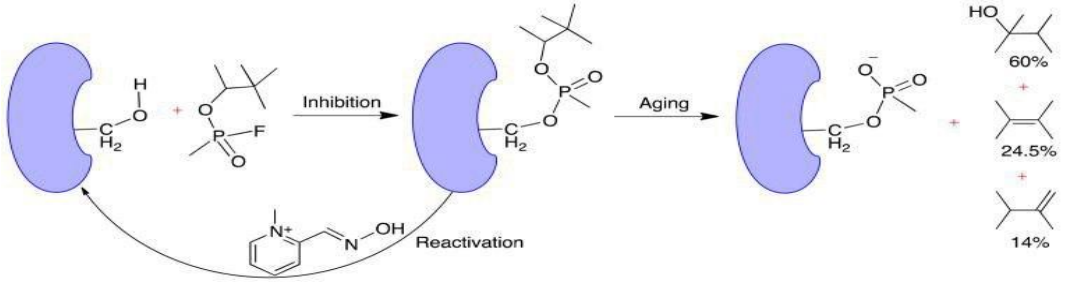
\Acetylcholine



Nonactivity acetylcholinesterase

In addition to primary inhibition of acetylcholinesterase (AChE), sarin indirectly affects other neurotransmitter and signaling systems, including modulation of GABAergic activity, alterations in ion channel function, and regulation of inflammatory pathways. Sarin exposure has also been associated with the development of delayed and chronic organophosphate-induced neurotoxicity, as well as effects on immune and endocrine regulation [8]. Standard therapy for poisoning is aimed at blocking the excessive action of acetylcholine (atropine), partially restoring AChE activity (oximes), and controlling seizures (diazepam) [8].

Mechanism of action of soman. Soman (3,3-dimethylbutan-2-yl methylphosphonofluoridate) contains a highly branched alkoxy group and is one of the most lethal nerve agents, with half-lives of 4.62 min and 1.87 min at pH 7 upon binding to AChE, respectively. Soman possesses two chiral centers, namely the phosphorus (P) atom and the Cα atom, and the stereochemistry at the phosphorus atom undergoes inversion during the formation of a covalent adduct between the soman molecule and the enzyme's active site.



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A schematic representation of the phosphorylation of acetylcholinesterase (AChE) by soman, subsequent reactivation by pralidoxime (2-PAM), and the ensuing irreversible aging process [6]. Using ab initio QM/MM molecular dynamics simulations based on the Born–Oppenheimer approach and employing the umbrella sampling method, the complete aging mechanism of soman-inhibited acetylcholinesterase (AChE) was characterized, and its free energy profile was determined. It was found that the aging process is favored when Glu199, located near the catalytic site, is protonated. Aging of the AChE–soman complex begins with cleavage of the covalent O_2–Cα bond, resulting in the formation of a 2,3-dimethylbutyl carbenium ion. In the transition state, the O2–Cα covalent bond is broken, and the migrating methyl group is distributed between the Cα and Cβ carbon atoms.

Immediately after bond cleavage, the negative charge formed on the phosphonate group is stabilized through the formation of a strong salt bridge with a reoriented imidazole ring. Subsequent migration of the methyl group following O2–Cα bond cleavage leads to the formation of a 2,3-dimethylbutyl carbenium intermediate.

Finally, the tertiary carbenium ion can be rapidly hydrated by a water molecule with the assistance of the hydroxyl group of Tyr121, resulting in the formation of 2,3-dimethyl-2-butanol. Overall, the aging of soman-inhibited acetylcholinesterase is an exothermic reaction and leads to the formation of a stable conjugate of aged acetylcholinesterase and 2,3-dimethyl-2-butanol as the major product, which is consistent with experimental findings [6].

Mechanism of action of VX. O-ethyl S-β-diisopropylaminoethyl methylphosphonate (VX) is an organophosphorus nerve agent with pronounced neuroparalytic activity. At room temperature, it is a colorless, oily liquid without odor (although some reports indicate that VX may exhibit a faint fruity odor, which is attributed not to the agent itself but to its impurities). VX, like other nerve agents, belongs to the group of highly potent cholinesterase inhibitors—enzymes responsible for the hydrolysis of acetylcholine into choline and acetic acid. Inhibition of this enzyme disrupts the regulation of acetylcholine levels and leads to its excessive accumulation in synapses, resulting in severe dysfunctions of the central and autonomic nervous systems.

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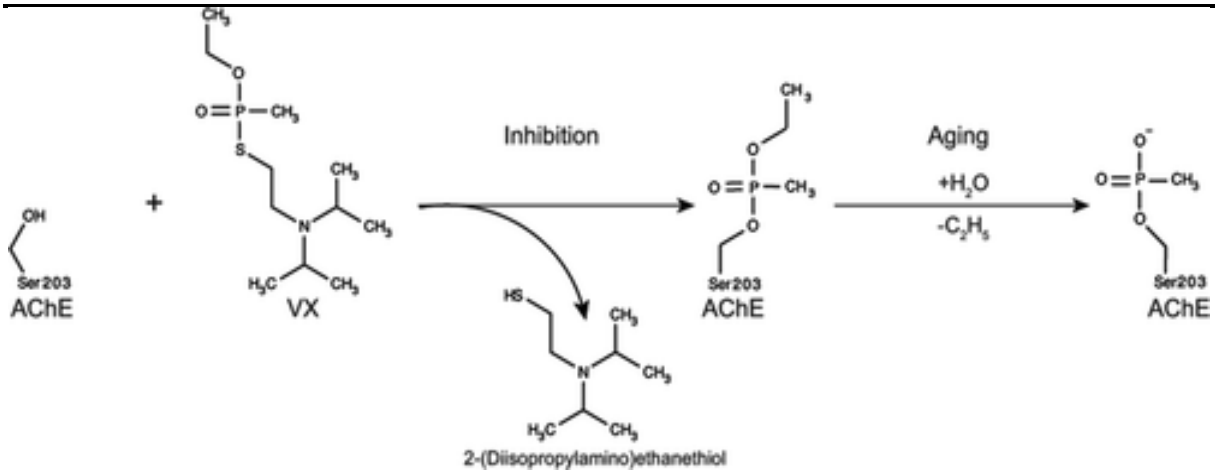

Inhibition and aging of VX in human acetylcholinesterase (hAChE)

Notably, [7] direct assessment of the key factors leading to inhibition of hAChE by V-series agents such as VX (O-ethyl S-β-diisopropylaminoethyl methylphosphonate) has traditionally been a challenging task, partly due to the limited availability of hAChE. Although structures of AChE from species other than humans inhibited by VX—such as mouse and Torpedo californica—are available, it is well known that the toxicity of nerve agents, including V-series compounds, varies in a species-dependent manner. This complicates direct comparison of nerve agent toxicity measured using homologs of hAChE. An additional level of complexity arises from the fact that the toxicity of nerve agents, including V-series compounds such as VX, has historically exhibited stereospecificity. Previous studies using human erythrocyte membranes revealed a 13-fold difference in toxicity between VX enantiomers, with the (−) or PX VX enantiomer being more toxic than its counterpart. Similar trends have been observed for other G- and V-series agents using comparable approaches with acetylcholinesterase from other species. Understanding the molecular basis of this stereospecific action of nerve agents, particularly in humans, remains limited in part due to the lack of structural data describing direct interactions between hAChE and the nerve agents themselves [7].

Despite the general similarity in their mode of action, the toxic mechanism of VX exhibits distinct features related to its chemical composition. VX is a heavier, low-volatility, and highly lipophilic organophosphorus compound, properties that

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allow it to persist longer on the skin and in the environment, evaporate more slowly, and exert prolonged inhibitory effects on acetylcholinesterase. In contrast, sarin is more volatile and less persistent. This results in a more rapid onset of action but a shorter duration of effect. Although enzyme inactivation by both agents is based on phosphorylation of the active site of cholinesterase, VX forms a more stable and less readily reversible bond, which accounts for the greater persistence of its toxic effects compared with sarin.

Thus, while the toxicodynamics of both compounds are governed by a common principle of cholinesterase inhibition, differences in their physicochemical properties determine distinct rates of intoxication development, environmental persistence, and duration of pathological effects.

Comparative analysis

Soman is characterized by high reactivity toward the catalytic serine of acetylcholinesterase, resulting in rapid formation of a phosphorylated enzyme complex. Its molecular structure, which includes two chiral centers and a bulky alkoxy group, enhances stereospecificity and influences the rate of enzyme binding. Kinetic parameters reported in studies indicate a high rate of interaction with AChE and relatively rapid formation of a stable adduct. Soman is also distinguished by an extremely rapid “aging” process—the chemical dealkylation of the phosphorylated enzyme that leads to complete loss of reactivatability by oximes. Aging proceeds through formation of a carbenium cation followed by hydration, yielding a stable product that irreversibly blocks the enzyme’s active site.

As a result, the therapeutic window for oxime administration in soman poisoning is minimal. Clinically, soman causes a rapid onset of cholinergic crisis with severe seizures and swift suppression of vital functions. Its toxicodynamics are determined not only by rapid binding and aging, but also by moderate lipophilicity, which обеспечивает sufficient tissue persistence while remaining less environmentally stable than VX.

Sarin also forms a phosphorylated adduct with acetylcholinesterase; however, its molecule is less bulky and more volatile than those of soman and VX, resulting

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in a different kinetic and toxicological profile. Enzyme phosphorylation occurs rapidly, but the resulting complex undergoes aging more slowly than in the case of soman.

This confers a relative therapeutic advantage, as the AChE adduct remains susceptible to oxime-mediated reactivation over a broader time window. Clinically, sarin produces a rapid but less prolonged toxic effect: due to its high volatility, it is readily absorbed via the respiratory tract and induces an acute cholinergic syndrome with pronounced autonomic and neuromuscular symptoms. However, its lower lipophilicity and reduced environmental persistence mean that it evaporates more quickly, less often causes prolonged contact exposure, and generally results in shorter-lasting effects than VX. The toxicodynamics of sarin are characterized by rapid onset, an intense but relatively short exposure phase, and a more favorable prognosis with timely antidotal therapy.

VX exhibits fundamentally different physicochemical properties that define its toxicological profile. It is highly lipophilic, poorly volatile, and oily in consistency, which ensures prolonged retention on skin, clothing, and surfaces, as well as slow percutaneous absorption. The kinetics of AChE inhibition by VX involve formation of a strong phosphorylated complex that, although it ages more slowly than the soman–AChE complex, often remains extremely stable and difficult to reactivate.

The stereospecificity of VX is more pronounced than that of sarin and soman, and differences between enantiomers can alter toxicity by orders of magnitude, complicating its biochemical characterization. High lipophilicity leads to prolonged absorption and extended toxicodynamics: the cholinergic crisis develops less rapidly than in inhalational sarin poisoning, but persists much longer and requires extended antidotal therapy and monitoring. The environmental and dermal persistence of VX significantly exceeds that of sarin and soman, making it particularly dangerous in contact exposure and complicating decontamination.

Comparative analysis demonstrates that although all three agents are AChE inhibitors with broadly similar biochemical targets, they differ fundamentally in their rates of enzyme interaction, aging kinetics, persistence, and toxicodynamics.

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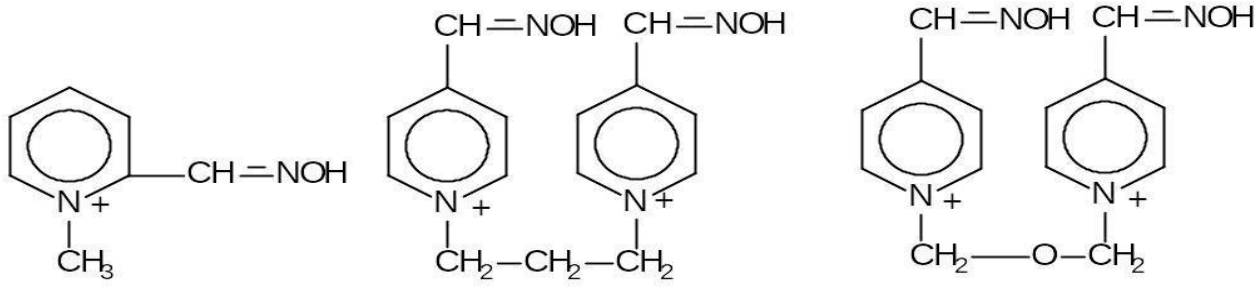
Soman exhibits the fastest aging and the narrowest therapeutic window; sarin shows slower aging, high volatility, and a relatively short exposure phase; VX demonstrates maximal lipophilicity, substantial persistence, and prolonged toxic exposure.

Agents for AChE reactivation

In addition to classical anticholinergic agents, pronounced central and peripheral anticholinergic effects are also exhibited by drugs from other pharmacological classes, including certain antipsychotics and antidepressants. The strongest anticholinergic activity is characteristic of thioxanthene and phenothiazine derivatives, such as chlorprothixene, aminazine (chlorpromazine), and fluoracizine, the latter being a component of prophylactic antidotes against nerve agents (P-6, P-10M). Additional enhancement of the protective effects of M-cholinolytics and reversible cholinesterase inhibitors is observed when combined with certain N-cholinolytic muscle relaxants, such as mecamylamine [10]. Reactivation of cholinesterase refers to the restoration of its catalytic function after blockade by organophosphorus compounds. Agents that accelerate this process are termed cholinesterase reactivators and act as biochemical antagonists of organophosphorus compounds. The first reactivating agents included hydroxylamine and hydroxamic acid derivatives; however, the most effective compounds proved to be oximes containing an oxime functional group. Classical representatives of this group include pralidoxime (2-PAM), dipiroxime (TMB-4), and toxogonin (LuH-6) [10].



2-ПАМ ТМБ-4 LuH-6

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The reactivation mechanism is based on a nucleophilic attack of the oxime group on the phosphorus atom of the phosphorylated enzyme, which leads to cleavage of the bond between phosphorus and the serine residue of the active site and to the formation of a phosphorylated oxime, accompanied by the release of the active enzyme. The efficiency of reactivation depends on the reaction rate and the maximum degree of enzyme recovery, which are determined by the structure of the organophosphorus compound, the properties of the reactivator, and the time elapsed since inhibition. For example, reactivation of erythrocyte cholinesterase inhibited by sarin under the action of 2-PAM occurs significantly faster than in the case of inhibition by DFP, which is associated with steric hindrance during the interaction of the oxime with bulky substituents of certain organophosphorus compounds.

The most active reactivators are bispyridinium compounds containing two pyridine rings, such as TMB-4 and toxogonin. Reactivators lacking pyridine fragments with quaternary nitrogen, for example diacetylaminoxime or isonitrosine, exhibit substantially lower antidotal activity, despite their ability to penetrate the blood–brain barrier.

Over time, phosphorylated cholinesterase becomes insensitive to the action of reactivators due to the process known as “aging” of the enzyme complex. Therefore, reactivators are effective only during the reversible phase of inhibition, the duration of which varies depending on the chemical structure of the organophosphorus compound. The most rapid aging is observed following inhibition by soman, rendering such complexes particularly resistant to reactivation.

Conclusion

A comparative analysis of the mechanisms of action of sarin, soman, and VX demonstrates that, despite a common mode of acetylcholinesterase inhibition, key differences in the rate of phosphorylation, the kinetics of enzyme aging, and physicochemical properties determine the severity and duration of the toxic effects of each compound [9]. Soman is characterized by the most rapid aging process and the narrowest therapeutic window; sarin exhibits slower dealkylation

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and greater susceptibility to reactivation [9], whereas VX is distinguished by high lipophilicity and prolonged toxic exposure. Comparative studies of organophosphorus compounds are of significant scientific and practical value, as they allow identification of structural factors that limit the effectiveness of existing oximes and thereby provide a basis for the development of more efficient antidotes. Such knowledge contributes to the design of new acetylcholinesterase reactivators, the selection of optimal combinations of antidotal therapy, and the improvement of treatment strategies for both acute and prolonged consequences of nerve agent poisoning.

ЛИТЕРАТУРА:

1. Каракчиев В. И. Военная токсикология и защита от ядерного химического оружия : учебное пособие. — М. : Воениздат, 1976. — 320 с.
2. Беспалов Ю. Г. Военная и экстремальная медицина : учебник для медицинских вузов. — СПб. : СпецЛит, 2008. — 512 с.
3. Гудман Л. С., Гилман А. Клиническая фармакология по Гудману и Гилману : в 2 т. Т. 1 / под ред. А. Г. Гилмана ; пер. с англ. — М. : Практика, 2006. — 1232 с.
4. Ахмеджанов Р. Р., Белоусов М. В. Медико-биологические основы безопасности жизнедеятельности. Часть I. Основы токсикологии : учебное пособие для вузов. — М. : Академия, 2005. — 256 с.
5. Куценко С. А. Основы токсикологии : учебник для студентов медицинских и биологических специальностей. — М. : Медицина, 2003. — 368 с.
6. Sirin G. S., Zhou Y., Raushel F. M. Aging mechanism of soman-inhibited acetylcholinesterase // Journal of Physical Chemistry B. — 2012. — Vol. 116, No. 9. — P. 2945–2954.
7. Wille T., Bester S. M., et al. Structural insights of stereospecific inhibition of human acetylcholinesterase by VX and subsequent reactivation by HI-6 // Chemical Research in Toxicology. — 2018. — Vol. 31, No. 11. — P. 1108–1117.
8. Mukherjee S., Gupta R. D. Organophosphorus nerve agents: types, toxicity, and treatments // Journal of Toxicology. — 2020. — Article ID 3007984. — 12

Modern American Journal of Medical and Health Sciences
ISSN (E): 3067-803X
Volume 2, Issue 1, January 2026
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p.
9. Mukherjee S., Gupta R. D., et al. Organophosphorus nerve agents: types, toxicity, and mechanisms // Frontiers in Pharmacology. — 2020. — Vol. 11. — Article 124.
10. Worek F., Thiermann H., Wille T. Organophosphorus compounds and oximes: a critical review // Archives of Toxicology. — 2020. — Vol. 94. — P. 2275–2292.