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A Brief Introduction to Nerve Agents

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Summary
In security policy, nerve agents are a relevant threat in chemical warfare, but also for attacks on individuals. The aim of this introduction is to provide basic historical, legal, medical and chemical knowledge of this complex matter for everyone who is interested in security policy and chemical warfare and to increase awareness. In the previous decade, attacks with the nerve agents sarin, VX and Novichok were reported. The weaponized nerve agents belong to the chemical group of organophosphates with four generations which block the enzyme acetylcholinesterase leading to a large variety of symptoms: The G-series, the V-series, the A-series (Novichoks) and the carbamates which are however currently not weaponized. The first chapter explains the mode of action and biochemical properties, then the history and the legal framework of the Chemical Weapons Convention. Thereafter, the symptoms and countermeasures are presented. The course of the resulting disease depends on the type of agent, the extent of exposure and the speed of therapeutic intervention. Rapid diagnosis and treatment are needed to limit damage and to prevent death, but also due to a chemical 'aging' process of the affected enzyme.
The medical treatment of nerve agents is embedded into other measures like physical protection, decontamination and triage and includes the imminent pre-hospital and the hospital treatment phases. The treatment is based on anticholinergics (atropine), acetylcholinesterase reactivation by oximes, anticonvulsive therapy with benzodiazepines and respiratory support to prevent respiratory failure as primary cause of death. New therapeutic concepts like bioscavengers are briefly discussed and summarized.

Contents

1. Introduction

In security policy, nerve agents are a relevant threat in chemical warfare, but also for attacks on individuals. The aim of this introduction is to provide basic historical, legal, medical and chemical knowledge of this complex matter for everyone who is interested in security policy and chemical warfare and to increase awareness. The first chapter explains the mode of action and biochemical properties, then the history and the legal framework of the Chemical Weapons Convention CWC. Thereafter, the symptoms and countermeasures are presented.

1.1 Chemical Class and Mode of Action

Toxic nerve agents are Organophosphates (OPs), organophosphorus molecules with the general structure O=P(OR)3 with a central phosphate molecule and alkyl or aromatic substituents or carbamates, but only OPs are still used as nerve agents. Effective organophosphates have a terminal oxygen connected to phosphorus by a double bond as a phosphoryl group, two lipophilic groups and a leaving group both bonded to the phosphorus. “R” stands for a variety of possible groups. Figure 1 shows the general structure of organophosphorus compounds with residues R1 and R2 and leaving group X.

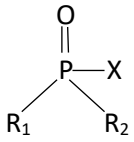

Figure 1 Organophosphate structure
Source: Worek et al. 2020, p.2278

The primary toxicity of organophosphates agents results from the permanent inhibition of the enzyme acetylcholinesterase (AChE) both in humans and insects. This is the reason why some substances like soman, VX and Novichok serve as nerve agents while other organophosphates like parathion and malathion serve as pesticides (insecticides). Organophosphate intoxication by nerve agents primarily results from inhalation or skin contact, while in farming the intoxication often is caused by chronic pesticide exposure.

The acetylcholinesterase is responsible for deactivating the neurotransmitter acetylcholine (ACh) and the related nerve signals. The acetylcholine receptor has two main variants, the nicotinic receptor, which is an ion channel for rapid effects and a muscarinic receptor which has metabolic effects via second messenger systems; thus all acetylcholine effects as well as the damage caused by nerve agents can be grouped into nicotinic, muscarinic and central (brain) effects. The organophosphate toxicity depends on the ability to access this acetylcholinesterase binding site (nerve agents bind serine 200, also known as 'esteric site'). The toxicity depends on size, shape and hydrophobicity of the nerve agent[1]. For example, when alkyl substituents increase in size and degrees of freedom, the toxicity decreases. The chiral orientation of the molecule also matters, for example the nerve agent soman exists as racemat where the S-enantiomers of are much more toxic than the R-enantiomers[2]. If the acetylcholinesterase is inhibited, acetylcholine accumulates in the synapse (nerve signal transmission space) and the overstimulation results in malfunction of nerves and muscles up to paralysis, convulsions and finally death. Treatment may counteract organophosphate effects (atropine), reactivate acetylcholinesterase (oximes), catch free organophosphate molecules (bioscavengers) or be supportive. Rapid diagnosis and treatment are needed to prevent damage and death, but also to avoid a so-called 'aging' process with irreversible dealkylation of the enzyme-OP complex may happen[3].

Another chemical class of acetylcholinesterase inhibitors are carbamates which temporarily block the acetylcholinesterase by carbomylation[4], but due to the temporary binding the intoxication is often less severe than for organophosphorus. Some carbamates are used as insecticides or in humans for stimulation of the cholinergic system in medicine, such as pyridostigmine bromide, while certain others can be very toxic. Therefore, carbamates were evaluated for use as chemical warfare agents during the Cold War, but never developed into chemical weapons[5]. The typical structure is shown in Figure 2.

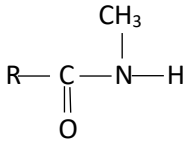

Figure 2 Carbamate Structure
Source: ATSDR 2007, p.21

1.2 History and Legal Framework

There are four types of toxic nerve agents, the G-series, the V-series, the Novichoks and the carbamates.

After the experience with chemical weapons in World War 1, the 1925 Geneva Protocol which prohibited the use of chemical and biological weapons, including poisonous gases,

[1] Sancho/Hemme 2019
[2] Sancho/Hemme 2019
[3] OPCW 2019, p.61
[4] NATO 2018, p.19-4
[5] Costanzi/Koblentz 2020

and of bacteriological methods of warfare. In 1932, the German chemist Willy Lange described the cholinergic nervous system effects of organophosphates and the German chemist Gerhard Schrader at company IG Farben inadvertently discovered in 1937 the first nerve agent with military potential, the ethyl-N-dimethyl-phosphoroamidocyanate, also known as tabun (GA).[6] The developments included sarin, tabun, and soman which were produced but not used during World War 2. American companies used the information from Schrader's laboratory to create OP pesticides such as Parathion.

In the 1950s, researchers in England produced a group of nerve agents later known as the V-series, which includes the chemical weapon VX, or O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothioate[7] which was much more toxic than the G series. The chemist Ranajit Ghosh at the company ICI intended to develop strong pesticides (organophosphate esters of substituted aminoethanethiols), one of them was marketed under the name Amiton[8] (or Tetram), but as it was too toxic, it was soon withdrawn from the market. The British Army developed then VX, Amiton was then named VG. Other countries produced homologues, e.g., the Russian Vx (or VR meaning Russian V-gas)[9]. In 1968, more than 6,000 sheep grazing near the US Army Dugway Proving Ground in Utah died during a VX field exercise[10].

During Cold War, several states, including the United States and the Soviet produced chemical weapons, including nerve agents. The largest quantities have been sarin and Vx (the Russian VX isomer O-isobutyl S-2-(diisopropylamino)ethyl methylthio-phosphonothiolate[11], also known as substance 33[12]). In the Iraq-Iran war from 1980 to 1988, sarin and tabun were used[13]. In March 1988, Iraq used the nerve agent sarin against the Kurdish village of Halabja in northern Iraq[14].

In 1992, the Chemical Weapons Convention (CWC), more precisely the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction was adopted and became effective in 1997 which forbids development, stockpiling, or use of any kind of chemical weapons[15]. Under the CWC, the Organization for the Prohibition of Chemical Weapons (OPCW) has established a verification and monitoring regime and a network of assistance and protection[16]. In 1995, the Japanese cult Aum Shinrikyo which owned sarin and VX gas attacked the city of Matsumoto in 1994 with 8 deaths and used sarin gas in the Tokyo subway system, resulting

[6] Johns Hopkins Center for Health Security 2013, p.1
[7] Shea 2013, p.2, Johns Hopkins Center for Health Security 2013, p.1
[8] Althoff 2018, p.7
[9] OPCW 2019, p.15, WHO 2004, p.174
[10] OPCW 2019, p.15
[11] WHO 2004, p.174
[12] Nepovimova/Kuca 2018, p.346. Chai et al. 2018 presented substance 33 which is a V-series molecule as Novichok nerve agent (Table 1)
[13] OPCW 2019, p.5
[14] OPCW 2019, p.17
[15] OPCW 2019, p.5
[16] OPCW 2019, p.6

in 13 deaths and more than 6,000 hospitalizations[17]. In Syria, sarin-containing rockets were used against several opposition-controlled or disputed areas of Ghouta in August 2013, with several hundreds of casualties[18]. In 13 February 2017, the nerve agent VX was sprayed against Kim Jong-nam, a half-brother of the North Korean leader Kim Jong-un, at Kuala Lumpur International Airport in Malaysia, who died later on[19].

The Novichok (Russian: "newcomer") agents were first published by the Russian chemists Wil Mirzayanov who worked at the State Scientific Research Institute for Organic Chemistry and Technology in Moscow and Lew Fjodorov in 1991 and 1992. These agents were developed in the early 1970ies, starting with N-2-diethylaminomethylacetoamidido-methylphosphonofluoridate or A-230[20]. It is assumed that this was part of a chemical weapon development program called Foliant[21]. Further agents which were included in Schedule 1 of the CWC were A-232 and A-234. On 04 March 2018, the former Russian agent Sergei Skripal and his daughter were poisoned by the Novichok nerve agent A-234 in Salisbury in Great Britain, but they survived[22]. A police officer who investigated the case was also exposed to this nerve agent. In June 2018, two further British citizens were inadvertently intoxicated by a Novichok-containing discarded perfume bottle, one of them died. The Russian politician Alexei Navalny was also poisoned with a Novichok nerve agent in August 2020[23]. While many details of the Novichok attacks are still under discussion, the medical case report for Nanvalny was published and will be briefly presented in Section 3.

Carbamates were evaluated for use as chemical warfare agents during the Cold War in the United States, but never developed into chemical weapons. In 2019, it was decided to include two toxic carbamate classes and the Novichoks into the Chemical Warfare Schedule 1 of the Chemical Weapons Convention CWC of 2020[24], see also Table 1 in the next Section 1.3. This schedule lists toxic chemicals only developed for or only used for chemical warfare[25]. However, the use of Novichoks and carbamate compounds as a weapon was already prohibited under the CWC[26].

1.3 Nerve Agent Series

There are four series (families) of nerve agents, the G-series, the V-series, the A-series (Novichoks) and the carbamate. Theoretically, the G-series and the V-series include several hundred different chemical substances[27], also dozens of Novichok chemicals and several carbamates would be possible. The CWC covers not only specific chemicals, but also

[17] OPCW 2019, p.17 and 20, Johns Hopkins Center for Health Security 2013, p.1
[18] OPCW 2019, p.19, Nikitin 2020, p.1
[19] Nikitin 2020, p.1
[20] Franc et al. 2019, p.2
[21] GDCH 2020, p.46
[22] Nikitin 2020, p.1
[23] Nikitin 2020, p.1
[24] Costanzi/Koblentz 2020
[25] de A Cavalcante SF 2020, p.2
[26] Nikitin 2020, p.1
[27] OPCW 2019, p.59

possible variants as shown in Table 1. The nerve agents are mostly odorless and colorless to yellow-brown liquids at ambient temperature. Some nerve agents may have a light odor as well, but when people can smell it, it means that they are already exposed[28]. The G- and the V-series are soluble in water and can be hydrolyzed, and the G-series can be vaporized by high temperatures and by explosions. Soman can be thickened by the addition of plastic substances to a sticky and persistent formulation[29]. The V-series agents are oily and persistent and can persist in a contaminated area for weeks[30]. Table 1 shows the G- and V-series as well as the Novichoks and carbamates that were listed in CWC Schedule 1 in 2020:

Nerve Agent	**Name (abbreviation)**	**Chemical Structure**
G-Series		O-Alkyl (<C10, incl. cycloalkyl) alkyl (Me, Et, n-Pr or i-Pr)-phosphonofluoridates
	Sarin, GB	O-Isopropyl methylphosphonofluoridate
	Soman, GD	O-Pinacolyl methylphosphonofluoridate
		Phosphoramidocyanidates; where R1 = (cyclo)alkyl with C<C10 and R2/R3 = Me, Et, i-Pr or n-Pr.
	Tabun, GA	O-Ethyl N,N-dimethylphosphoramidocyanidate
V-Series		O-Alkyl (H or <C10, incl. cycloalkyl) S-2-dialkyl (Me, Et, n-Pr or i-Pr)-aminoethyl alkyl (Me, Et, n-Pr or i-Pr) phosphonothiolates and corresponding alkylated or protonated salts
	VX	O-Ethyl S-2-diisopropylaminoethyl methylphosphonothiolate
A-Series	Novichoks	
	A-230	P-alkyl (H or ≤C10, incl. cycloalkyl) N-(1-(dialkyl(≤C10, incl. cycloalkyl)amino))alkylidene(H or ≤C10, incl. cycloalkyl) phosphonamidic fluorides and corresponding alkylated or protonated salts e.g. N-(1-(di-n-decylamino)-n-decylidene)-P-decylphosphonamidic fluoride Methyl-(1-(diethylamino)ethylidene)phosphonamidofluoridate, known as A-230
	A-232 and A-234	O-alkyl (H or ≤C10, incl. cycloalkyl) N-(1-(dialkyl(≤C10, incl. cycloalkyl)amino))alkylidene(H or ≤C10, incl. cycloalkyl) phosphoramido-fluoridates and corresponding alkylated or protonated salts, e.g. O-n-Decyl N-(1-(di-n-decylamino)-n-decylidene)phosphoramidofluoridate Methyl (1-(diethylamino)ethylidene)phosphoramidofluoridate, known as A-232 Ethyl (1-(diethylamino)ethylidene)phosphoramidofluoridate, known as A-234
	others	Methyl-(bis(diethylamino)methylene)phosphonamidofluoridate
Other	Carbamates	Quaternaries of dimethylcarbamoyloxypyridines: 1-[N,N-dialkyl(≤C10)-N-(n-(hydroxyl, cyano, acetoxy)alkyl(≤C10)) ammonio]-n-[N-(3-dimethylcarbamoxy-α-picolinyl)-N,N-dialkyl(≤C10) ammonio]decane dibromide (n=1-8), e.g. 1-[N,N-dimethyl-N-(2-hydroxy)ethylammonio]-10-[N-(3-dimethylcarbamoxy-αpicolinyl)-N,N-dimethylammonio]decane dibromide
		Bisquaternaries of dimethylcarbamoyloxypyridines: 1,n-Bis[N-(3-dimethylcarbamoxy-α-picolyl)-N,N-dialkyl(≤C10) ammonio]-alkane-(2,(n-1)-dione) dibromide (n=2-12), e.g. 1,10-Bis[N-(3-dimethylcarbamoxy-α-picolyl)-N-ethyl-N-methylammonio]decane-2,9-dione dibromide

Table 1 Nerve Agent Series
Source: OPCW 2019, p.60, current CWC Schedule 1

For G-series nerve agents, such as sarin, the inhalation toxicity is significantly greater than the dermal toxicity. Thus, G-agents are primarily designed for inhalation, while the much more toxic V-agents primarily penetrate through the skin, but can be also absorbed through

[28] Shea 2013, p.2, Johns Hopkins Center for Health Security 2013, p.1
[29] EMEA 2003, p.11
[30] EMEA 2003, p.11, OPCW 2019, p.60

the respiratory and gastrointestinal tracts, as well as conjunctivae. Aerosolized V-series agents might penetrate personal semipermeable, protective clothing[31].

The Novichok (Russian: "newcomer") were developed in the early 1970ies, starting with N-2-diethylaminomethylacetoamidido-methylphosphonofluoridate or A-230, which was a sarin derivative where the O-isopropyl group was replaced by the acetoamydin radical[32]. Based on A-230, four further Novichoks were synthesized: A-232 and A-234 (respectively the methoxy and ethoxy analogues of A-230) and A-242 and A-262 (the guanidine analogues of A-230 and A-232, respectively) [33]. A-230, A-232, and A-234 are liquids, while A-242 and A-262 are the first nerve agents known to be in the solid state at room temperature[34]. Novichok-5 is a binary analog of A-232, 8 times more effective than VX while Novichok-7 is a binary analog of A-234, 10 times more effective than soman[35]. So far, only A-230 was weaponized in 1990[36]. According to available literature, Novichoks are typically more toxic than VX[37]. Their different molecular structure may make them more difficult to detect by standard NATO chemical-detection equipment and may easier penetrate defeat chemical-protective gear[38].

Carbamates temporarily block the acetylcholinesterase by carbomylation[39]. With respect to carbamates, the severity of carbamate poisoning tends to be less than that for organophosphorus compounds, as they typically bind the acetylcholinesterase only temporarily. The duration of toxicity also tends to be shorter for most patients; on the order of 6-12 hours[40]. Some carbamates are very toxic and listed in the Chemical Warfare CWC Schedule 1 while the carbamate-based medication pyridostigmine bromide (Mestinon) can be used as pre-treatment for soman intoxication.

1.4 Production

Nerve agent production requires the use of toxic chemicals during synthesis and specialized equipment to contain the nerve agents produced, but the chemicals are usually less toxic than the nerve agent itself[41]. In the 1980ies, binary weapons were developed where less toxic chemicals are mixed to form nerve agents shortly before release (such as artillery shell, rocket, or aerial bomb)[42]. Binary chemical weapons are less dangerous to manufacture, transport, and handle, but the resulting nerve agent may then be less pure or effective then[43]. The first binary weapons developed by the USA were GB-2, GD-2, and

[31] OPCW 2019, p.61
[32] Franc et al. 2019, p.2
[33] Franc et al. 2019, p.2
[34] Franc et al. 2019, p.7
[35] Chai et al. 2018, Table 1
[36] Nepovimova/Kuca 2018, p.346
[37] Franc et al. 2019, p.8
[38] WHO 2004, p.174
[39] NATO 2018, p.19-4
[40] ATDSR 2007, p.79
[41] Shea 2013, p.2
[42] OPCW 2019, p.17
[43] Shea 2013, p.2

VX-2, the binary versions of sarin, soman, and VX, respectively and were called the third generation of chemical weapons[44]. For attacks on individuals, nerve agents could be sprayed.

2. Nerve Agent Intoxication – Symptoms and Course

The course of the resulting disease depends on three factors: the type of agent, the extent of exposure and the speed of therapeutic intervention. Organophosphate intoxication by nerve agents primarily results from inhalation or skin contact, while in farming the intoxication often is caused by chronic pesticide exposure. Organophosphates can be absorbed by all routes, including inhalation, ingestion, and dermal absorption, for toxic nerve agent inhalation and skin contact are the primary routes. They bind and block the acetylcholinesterase which is responsible for deactivating the neurotransmitter acetylcholine resulting in acetylcholine accumulation a subsequent malfunction of nerves with convulsions and blockade of muscles. The first symptoms usually appear within seconds of exposure.

The acetylcholine receptor (AChR) has two main variants, the nicotinic receptor that is in particular present in ganglia of the autonomous nerve system and skeletal muscles, which is an ion channel for rapid effects, and a muscarinic receptor that is in particular present in the parasympathetic nerve system and smooth muscles which has metabolic effects via second messenger systems. Both receptor variants are present in the Central Nervous System (CNS), i.e., the brain, so all acetylcholine effects as well as the damage caused by nerve agents can be grouped into nicotinic, muscarinic and central (brain) effects.

Smooth muscles, exocrine glands and heart muscle are controlled by a balanced system of sympathetic norepinephrine and parasympathetics acetylcholine to control physiologic stress and rest situations. For nerve agents it means that very early norepinephrine (adrenalin-like) disturbances may occur with mydriasis (smooth eye muscles), hypertension (blood vessels) and tachycardia (heart muscle) while then the muscarinic-parasympathetic symptoms dominate very rapidly, also known as cholinergic toxidrome[45].

Muscarinic symptoms are primarily those caused by overactive glands and smooth muscles, while nicotinic symptoms affect the skeletal muscles (blockade of neuromuscular junction at the motor end plate) and the circulation which is controlled by the autonomic ganglia. The earliest muscarinic symptoms are the so-called ‘wet signs’: salivation, lacrimation, urination, and defecation, followed by a dominance of parasympathetic symptoms: bradycardia, hypertension, muscular twitching, fasciculations, weakness, and paralysis[46]. In the Novichok attack of 2020, a new symptom, a severe hypothermia down to 33.5°C was reported[47].

[44] Franc et al. 2019, p.3
[45] ATDSR 2007, p.25ff.
[46] OPCW 2019, p.127
[47] Steindl et al 2020, p.1

Central nervous system signs and symptoms are non-specific and can suggest mental illness. They are caused by complex effects and both nicotinic and muscarinic receptors and can show a large variety of symptoms. The death is typically caused by a respiratory failure, caused by a combination of bronchoconstriction, bronchorrhea, central respiratory depression and weakness and paralysis of respiratory muscles.[48] Case reports of neuropsychological long-term damage such as posttraumatic stress disorder (PTSD), anxiety and depressive symptoms exist.

3. Countermeasures

The drug treatment of nerve agents is embedded into other measures like physical protection, decontamination and triage and can be differentiated into the imminent pre-hospital treatment, the hospital treatment and long-term treatment phases. After becoming aware of an attack, treatment should start as soon as possible. Evacuation and decontamination should take place followed by appropriate hospital treatment.

Ideally, military detection systems ranging from manually operated wet chemical detection kits to advanced automatic equipment for specific chemical warfare agents are already in place to allow immediate alarming in case of an attack. Irrespective of the chemical weapon used, primary measures include agent detection and identification, protection and decontamination. In case of mass exposures, triage should be used to prioritize certain patients[49]

Irrespective of the chemical weapon used, primary measures include agent detection and identification, protection and decontamination, as well as entry control to potentially affected areas divided into exclusion or hot zone for the incident area, contamination reduction or warm zone with decontamination stations and corridor and the support/cold zone with control lines[50]. Decontamination (such as clothing removal, eye rinsing with physiological saline solution and skin cleaning with soapy water, if no special solutions are available) is also needed to avoid inadvertent spreading to medical personnel and triage in case of mass attacks, then specific antidote therapy and symptomatic treatment as applicable[51].

The treatment is based on four pillars: anticholinergics (atropine), acetylcholinesterase reactivation by oximes, anticonvulsive therapy with benzodiazepines and respiratory support to prevent respiratory failure as primary cause of death. The primary treatment goal is a sufficient control of clinically significant symptoms by a stepwise dose escalation (‘titration’). Meanwhile, military autoinjectors with atropine/pralidoxime and diazepam simplify emergency uses.

Atropine blocks acetylcholine at muscarinic receptors and mitigates the nerve agent effects. The OPCW, NATO and the European Medicines Agency EM(E)A fully agree that the

[48] ATDSR 2007, p.43
[49] OPCW 2019, p.27-28 and 64 and EMEA 2003, p.12
[50] OPCW 2019, p.23 and 33
[51] OPCW 2019, p.23 and 36

treatment goal is a sufficient control of clinically significant symptoms (reversal of the '3Bs' bradycardia, bronchospasm and bronchorrhea [respiratory secretions][52]) by a stepwise atropine dose escalation ('atropine titration') with a minimum interval of 5 minutes until next dosing.[53] Atropine has little effect on nicotinic (e.g., muscular) symptoms, while oximes can unlock the blocked acetylcholinesterase by a chemical reaction and by this revert the effect of the nerve agent[54]. The benzodiazepine diazepam is an effective anticonvulsant. Respiratory support including intubation and mechanical ventilation is particularly important, since respiratory failure is the usual cause of death[55].

In late 2020, the first report on Novichok treatment was published[56]. In August 2020, the Russian citizen Navalny suddenly became confused and began to sweat heavily, vomited, collapsed, and lost consciousness. After treatment in Omsk and Berlin, he recovered after several weeks. This first case report indicated that atropine is effective against Novichoks while the oxime obidoxime was not. Respiratory support, sedation and an administration of fresh frozen plasma were additional measures that finally led to recovery.

New concepts are bioscavengers like human butyrylcholinesterase that bind nerve agents in blood, catalytic scavengers that rapidly hydrolyze nerve agent molecules and α7-nicotinic acetylcholine receptor agonists which improve neurocognitive functions and mitigate neuroinflammation. Bioscavengers such as the human butyrylcholinesterase (BChE) quickly bind with nerve agents[57]. If a reactivator like an oxime is given additionally, the oximes can 'take over' the nerve agent from the scavenger which is then free for further activities again. This two-component system is called pseudo-catalytic scavenger. Another approach are catalytic scavengers that rapidly hydrolyze nerve agent molecules to non-toxic products such as the enzyme paraoxonase (PON-1)[58]. However, issues with production, stabilization and pharmacokinetics affect the practical use is still affected by technical problems. An alternative could be fresh frozen plasma (FFP) to increase the excretion of nerve agent[59].

Nicotinic acetylcholine receptors (nAChRs) are affected by nerve agents in the brain and the autonomic ganglia[60]. In particular, α7 nAChRs are critical for cognition, sensory processing, attention, working memory, and reward[61]. Also α7-nicotinic AChR agonists also may alleviate some of the inflammatory damage during the initial stages of OP poisoning by suppressing cytokine release from glia macrophages (while antagonists seem

[52] Hulse et al. 2019, p.460. Note that the EMEA was meanwhile renamed to EMA, but the older documents are still coded EMEA.
[53] NATO 2018, p.19-9, OPCW 2019, p.66 and 67
[54] ATDSR 2007, p.87
[55] ATDSR 2007, p.69
[56] Steindl et al. 2020, p.1-4
[57] Masson/Nachon 2017, p.27-28
[58] Masson/Nachon 2017, p.31
[59] Peter/Moran et al. 2008, p.340
[60] Sheridan 2005, p.144
[61] Yang et al. 2017, p.612

to enhance inflammation)[62]. But again, pharmacokinetic and selectivity problems[63] are hurdles for practical use.

4. Summary

In the previous decade, attacks with the nerve agents sarin, VX and Novichok were reported demonstrating the relevance of nerve agents and their treatment. The currently weaponized nerve agents belong to the chemical group of organophosphates (OPs) and exert their effects by inhibition of the enzyme acetylcholinesterase which leads to muscarinic, nicotinic and central symptoms: The G-series with sarin, soman and tabun, the V-series with VX and the A-series (Novichoks) which were used in two attacks on individuals in 2018 and 2020 and are characterized by a new molecular structure and a high toxicity. Another chemical group, the carbamates, is also covered by the Chemical Weapons Convention, but currently not weaponized.

The primary cause of death is respiratory failure and rapid intervention is necessary. The treatment is based on four pillars: anticholinergics (atropine), acetylcholinesterase reactivation by oximes, anticonvulsive therapy with diazepam and respiratory support. Meanwhile, military autoinjectors with atropine/pralidoxime and diazepam simplify emergency uses. The dosing recommendations of the institutions slightly differ but the primary treatment goal is a sufficient control of clinically significant symptoms by a stepwise dose escalation ('titration'). The first published case report of Novichok intoxication indicates that atropine is also effective against Novichoks. New concepts like bioscavengers such as the human butyrylcholinesterase (BChE), catalytic scavengers like the enzyme paraoxonase (PON-1) and α7-nicotinic acetylcholine receptor agonists still face high pharmacological and technical hurdles for practical use. However, they remain a promising research target for mitigation of nerve agent damage symptoms.

5. Literature

ATSDR (2007) Agency for Toxic Substances and Disease Registry Case Studies in Environmental Medicine Cholinesterase Inhibitors: Including Pesticides and Chemical Warfare Nerve Agents. Course: WB1102 CE Original Date: October 17, 2007, 153 pages

Banks CN and Lein PJ (2012): A Review of Experimental Evidence Linking Neurotoxic Organophosphorus Compounds and Inflammation. Neurotoxicology. 2012 June; 33(3): 575–584. doi:10.1016/j.neuro.2012.02.002

de A Cavalcante SF, Simas BC, Barcellos MC, de Oliveira GM, Sousa RB, de M Cabral PA, Kuca K, and Franç TCC (2020) Acetylcholinesterase: The "Hub" for Neurodegenerative Diseases and Chemical Weapons Convention. Biomolecules 2020, 10, 414; doi:10.3390/biom10030414

Chai PR, Hayes BF, Erickson TB, and Boyer EW (2018): Novichok agents: a historical, current, and toxicological perspective. Toxicol Commun. 2018; 2(1): 45–48. doi:10.1080/24734306.2018.1475151

Costanzi S and Koblentz GD (2020) Updating the CWC: How We Got Here and What Is Next. Arms Control Today online April 2020

[62] Banks/Lein 2012, Section 2.0 and 7.0
[63] Yang et al. 2017, p.616-617

EMEA (2003) EMEA/CPMP Guidance document on use of medicinal products for treatment of patients exposed to terrorist attacks with chemical weapons. Document No. CPMP/1255/03, 25 April 2003. London, United Kingdom: European Medicines Agency.

Franç TCC, Kitagawa AS, de A Cavalcante SF, da Silva JAV, Nepovimova, E and Kuca K (2019) Novichoks: The Dangerous Fourth Generation of Chemical Weapons. Int. J. Mol. Sci. 2019, 20, 1222; doi:10.3390/ijms20051222

GDCH (2020): Chemikalienregulierung - Ein unbekanntes Nervengift Nachrichten aus der Chemie Nr. 68 September 2020, p.45-48

Hulse EJ, Haslam JD, Emmett SR and Woolley T (2019): Organophosphorus nerve agent poisoning: managing the poisoned patient. British Journal of Anaesthesia, 123 (4): 457e463 (2019)

Johns Hopkins Center for Health Security (2013) Nerve Agents Fact Sheet

Masson, P and Nachon F (2017) Cholinesterase reactivators and bioscavengers for pre- and post-exposure treatments of organophosphorus poisoning Special issue XVth International Symposium on Cholinergic Mechanisms of the International Society for Neurochemistry, J. Neurochem. (2017) 142 (Suppl. 2), 26--40

NATO (2018) Nato Standard AMedP-7.1. Medical Management of CBRN Casualties. Edition A Version 1, June 2018

Nepovimova E, Kuca K (2018) Review: Chemical warfare agent NOVICHOK - mini-review of available data. Food and Chemical Toxicology 121 (2018) 343–350
https://doi.org/10.1016/j.fct.2018.09.015

Nikitin, MBD (2020) Resurgence of Chemical Weapons Use: Issues for Congress Updated September 18, 2020 Congressional Research Service CRS Insight Report IN10936

OPCW (2018) Organophosphorus (OP) Nerve Agents and Countermeasures. OPCW Poster 08/2018, one page

OPCW (2019) Practical Guide for Medical Management of Chemical Warfare Casualties of the OPCW Organization for the Prohibition of Chemical Weapons International Cooperation and Assistance Division Assistance and Protection Branch, 164 pages

Sancho SS and Hemme M (2019) Acetylcholinesterase Inhibition. OPCW Poster 01/2019, one page

Shea, DA (2013) Chemical Weapons: A Summary Report of Characteristics and Effects. Congressional Research Service CRS Report R42862 from 13 September 2013

Sheridan RD, Smith AP, Turner SR, Tattersall JEH (2005) Nicotinic antagonists in the treatment of nerve agent intoxication J R Soc Med 2005;98:114–115

Steindl D, Boehmerle W, Körner R, Praeger D, Haug M, Nee J, Schreiber A, Scheibe F, Demin K, Jacoby P, Tauber R, Hartwig S, Endres M, Eckardt KU (2020) Novichok nerve agent poisoning. Case Report Lancet online December 22, 2020 https://doi.org/10.1016/S0140-6736(20)32644-1

WHO (2004) Public health response to biological and chemical weapons—WHO Guidance Annex 1: Chemical Agents, p.144-213

Worek F, Thiermann H and Wille T (2020) Organophosphorus compounds and oximes: a critical review Archives of Toxicology (2020) 94:2275–2292 https://doi.org/10.1007/s00204-020-02797-0

Yang T, Ting X, Qi S and Wang K (2017) The current agonists and positive allosteric modulators of α7 nAChR for CNS indications in clinical trials Acta Pharmacologica Sinica B 2017; 7(6):611-622 http://dx.doi.org/10.1016/j.apsb.2017.09.001