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Chemical toxins that cause seizures

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A B S T R A C T

Seizurogenic chemicals include a variety of toxic agents, including chemical warfare agents, toxic industrial chemicals, and natural toxins. Chemical weapons such as sarin and VX, and pesticides such as parathion and carbaryl cause hyperstimulation of cholinergic receptors and an increase in excitatory neurotransmission. Glutamatergic hyperstimulation can occur after exposure to excitatory amino acid toxins such as the marine toxin domoic acid. Other pesticides such as lindane and strychnine do not affect excitatory neurotransmission directly, but rather, they block the inhibitory regulation of neurotransmission by antagonism of inhibitory GABA and glycine synapses. In this paper, chemicals that cause seizures by a variety of molecular mechanisms and pathways are discussed.

1. Introduction

Neuronal hyperactivity in the brain and the peripheral nervous system can lead to various acute and long-term pathologies. These abnormalities can cause at best a poorer quality of life, and at worst, serious illness and death. Primary manifestations of abnormally high neuronal activity are seizures and convulsions. These symptoms can be debilitating and can result in serious acute injury. A common cause of seizures is the epilepsies that afflict millions of people worldwide. It is estimated that 10% of adult Americans will suffer from a seizure during their lifetime (American Epilepsy Foundation, www.epilepsyfoundation.org). Seizures usually cause a loss of consciousness. When the patient does not regain consciousness between seizures, or the seizures last for more than 30 min, the term status epilepticus (SE) is used. The seizures can vary in the level of severity and be generalized or focal within the brain. Symptomatic epilepsy and seizures can be caused by many factors such as brain malformations, metabolic and genetic disorders, drug use, infection, head trauma, stroke and other disorders. Sometimes seizures are cryptogenic and have no clear underlying cause.

Another important cause of seizures is exposure to toxic chemicals that cause excessive hyperactivity in the nervous system. Some household chemicals are capable of producing seizures if exposure occurs at high enough doses, but the majority of human exposures to seizurogenic chemicals comes from industrial accidents, misuse in agriculture, or occupational hazards. The list of seizurogenic chemicals is quite diverse and includes toxic industrial chemicals, pesticides, and natural toxins (Table 1). The diversity of this list of chemicals is not only in their origin and use, but also in their molecular mechanisms of action on excitable cells.

An important consequence of seizures induced by disease or chemicals is the short- and long-term neuropathology caused by excitotoxicity. After the initial increase in stimulatory neuronal activity, or a decrease in activity at inhibitory synapses that results in unregulated hyperactivity, the excitotoxic process first involves the stimulation of glutamate and other post-synaptic excitatory amino acid ionotropic receptors that cause abnormal membrane permeability of ions, especially Ca++. This causes eventual calcium accumulation, increased catabolic activity, and neuronal injury and neuronal death. The acute phase can be followed by longer term regional neurodegeneration that can have functional consequences, ranging from subtle cognitive decline to sensory and motor deficits. Research on safe and effective anti-glutamatergic drugs and prevention of neurodegeneration will be critical for protecting against long-term effects of chemicals that induce seizures.

2. Cholinesterase inhibitors

A large class of chemicals that are very toxic to humans and cause seizures and convulsions are the pesticides and chemical warfare agents that inhibit the hydrolytic enzyme acetylcholinesterase (AChE) (BC 3.1.1.7). This class includes over 200 compounds. Organophosphorus (OP) nerve agents developed for chemical warfare during World War II also are the most notorious seizurogenic compounds. These include the highly toxic VX and sarin “nerve gases” (Table 1), even though they are actually liquids at ambient temperatures (Rodgers and Condurache, 2010). OP pesticides represent one of the largest classes of insecticides used
Table 1
Examples of chemical agents that cause seizures and mechanisms of their actions.

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Chemical class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemicals that increase excitatory neurotransmission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition of acetylcholinesterase and hyper-stimulation of cholinergic receptors</td>
<td>Organophosphorus and Carbamate pesticides</td>
<td>Parathion, chlorpyrifos, aldicarb, carbaryl</td>
</tr>
<tr>
<td></td>
<td>Chemical warfare agents</td>
<td>Sarin, soman and VX</td>
</tr>
<tr>
<td></td>
<td>Organochlorine and Pyrethroid pesticides</td>
<td>DDT, permethrin, fenvalerate</td>
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<tr>
<td></td>
<td>Biotoxins</td>
<td>Strychnine</td>
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<td></td>
<td>Excitotoxic Amino Acids</td>
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<tr>
<td></td>
<td>Industrial chemicals</td>
<td>Cyanide, azide</td>
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<tr>
<td><strong>Chemicals that decrease inhibitory neurotransmission</strong></td>
<td></td>
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<tr>
<td>GABA receptor inhibition</td>
<td>Pesticides</td>
<td>Lindane, tetramethylenedisulfo-tetramine</td>
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<tr>
<td></td>
<td>Biotoxins</td>
<td>Picrotoxin</td>
</tr>
<tr>
<td></td>
<td>Pesticides</td>
<td>Strychnine</td>
</tr>
</tbody>
</table>

a Dichlorodiphenyl-trichloroethane.
b β-N-methylamino-ε-alanine.
c β-N-oxalamino-ε-alanine

3. Seizurogenic chemicals that modulate ion channels

Another class of pesticides called organochlorines can cause seizures. These pesticides were banned from use in the United States in the 1970s because of their effects on wildlife, however, DDT (dichlorodiphenyltrichloroethane) is still a major component of programs to eradicate mosquito larvae, and is still used as a human delousing agent and as an inexpensive agricultural insecticide in some parts of the world. DDT interferes with the function of sodium channels by prolonging the falling phase of the action potential, leading to repetitive firing of the nerve impulse, tremors and seizures (Chang and Dyer, 1995). Unlike the organophosphates, there are no specific antidotes for organochlorine pesticides. Severe acute exposure to these compounds is usually treated with benzodiazepines as a first-line therapy, followed by phenobarbital and propofol infusions, depending on if the seizures are refractory or recurring.

Another more popular class of insecticides in use today is the pyrethroids. The pyrethroids and DDT have similar effects on voltage-gated sodium channels. The action of pyrethroids on sodium channels causes repetitive neuronal discharge and neuronal hyper-excitability characteristics of other nerve excitants (Bradberry et al., 2005), and would be treated medically in a similar manner to other seizurogenic toxins. At high enough doses, these compounds can also inhibit the inhibitory effects of gamma-aminobutyric acid (GABA). Fortunately the pyrethroids are far less toxic to mammals than they are to insects, but accidental and some occupational exposures to high doses are of concern.

Chemicals derived from biological sources are also capable of modulating ion channels and cause hyperpolarization and seizures. Some of the scorpion toxins are peptides that bind to sodium channels and enhance activation of the channel or slow its inactivation component (Catterall et al., 1976; Leipoldt et al., 2012). Ciguatoxins and brevetoxins are produced by marine microorganisms and also have a dual mechanism of enhancing activation and slowing inactivation of sodium channels (Lombert et al., 1987). Anatoxin is another marine toxin produced from cyanobacteria that is a potent agonist of the nicotinic acetylcholine receptor ion channel (Daly, 2005). This toxin can produce excessive salivation, tremors, and seizures.

A primary excitatory neurotransmitter in the nervous system is glutamate, and there are several excitatory amino acid (EAA) toxins that can cause seizures. Kainic acid and a similar EAA, domoic acid activate NMDA and AMPA subtypes of glutamate receptors, and cause an influx of excessive calcium. Other less common EAAs include BMAA and BOAA (Table 1) that are excitotoxins by way of stimulating these types of glutamate...
receptors. There are no specific antidotes yet for most of the biologically derived toxins that cause seizures, and most are treated mainly with supportive care. For example treatment for severe shellfish poisoning involves fluid replacement and pain management. Several laboratories are studying the molecular mechanisms of these toxins in hopes of finding antagonists or other modes of reversing their toxic effects at the sites of action (Gerwick and Moore, 2012; Payandeh et al., 2012).

4. Toxins that disrupt inhibitory neurotransmission

Normal neurotransmission is regulated by inhibitory neurotransmitters and receptors as a counterbalance to excitatory neurotransmission. Toxins that block this inhibitory control can cause seizures. Similar to the insecticide lindane, the rat poison TETS (tetramethylenedisulfide-tetramine) binds to sites on receptors of the inhibitory neurotransmitter GABA, and block its inhibitory function. The highly toxic plant compound picrotoxin is a noncompetitive antagonist of the GABA receptor as well, and is used in models of status epilepticus to study seizures (Baden et al., 2005). Exposure to this compound can result in neuronal activation, tremor and convulsion. Strychnine is a plant alkaloid that is a convulsant because it is an antagonist of receptors that bind the inhibitory neurotransmitter glycine, mostly in the spinal cord. These actions can cause hyperactivity of both sensory and motor functions (Philippe et al., 2004). Aggressive airway management and anticonvulsants, as well as neuromuscular blockade in some cases are required for successful treatment of strychnine poisoning.

5. Cyanide

Among the most toxic industrial chemicals with clinically significant impact on the nervous system, is the metabolic poison cyanide. Cyanide is toxic ultimately in its ionic form (CN\(^{-}\)) that can be released from hydrogen cyanide or cyanogen chloride gases. It can also come from sodium, potassium and calcium salts that when mixed with acid, release highly toxic hydrogen cyanide vapor. Neurological symptoms after acute exposure to cyanide usually include headache, vertigo, and seizures, followed by coma, respiratory failure, cardiac arrest and death. Cyanide may cause neurodegeneration by its effect on mitochondrial respiration, but there is evidence that other molecular mechanisms may be involved such as excitotoxicity and interaction with inhibitory neurotransmitters (Dawson et al., 1995).

At present there are two cyanide-specific antidotes. The Cyanokit\textsuperscript{R} contains hydroxocobalaminst, a vitamin B12 relative that binds free cyanide in the blood stream. The Nithiodote\textsuperscript{R} product contains sodium nitrite and sodium thiosulfate, both of which aid in the detoxification of cyanide. All of the current antidotes for cyanide are not without limitations related to safety and ease of use in the field. However there are promising candidates under development with better safety profiles that can be administered easily in the field (Belani et al., 2012; Chan et al., 2010).

6. Conclusions

Several thousand chemicals from natural and industrial sources are highly toxic and can have deleterious effects on human health. These chemical affect a variety of organ systems and some can have very specific mechanisms that underlie their lethal effects. Some chemicals are toxic to the nervous system by causing hyperactive neurotransmission. This may be due to overstimulation of excitatory synapses, or the inhibition of inhibitory synapses. In both cases, the resultant increase in neuronal activity causes seizures and convulsions. These effects can be lethal if they persist and cause a depletion of cellular energy stores, or they can cause long-term neuronal damage in survivors. Current and next generation anticonvulsants and neuroprotectants are possible medical interventions that can counteract the seizurogenic activity of chemical toxins, but caution must be taken that the therapeutics can be used safely in the presence of chemical toxins that could have secondary effects. In some cases removal of the toxin from circulation before lethal amounts reach the cellular or tissue targets can be effective. In other cases, in vivo detoxification mechanisms are the primary mode of defense and the only chance of survival, given that exposure is below lethal levels that overwhelm this process.

Conflict of interest statement

None.

References

Leipoldt E, Borges A, Heinemenn SH. Scorpion beta-toxin interference with Na\(^{+}\) channel voltage sensor gives rise to excitatory and depressant modes. J Gen Physiol 2012;139:305–19.