Toxic responses of the nervous system

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Lec 1,2
Neuron

- Dendrite
- Cell body
- Myelin sheath (Schwann cell)
- Node of Ranvier
- Axon
- Axon terminals
Support cells

In CNS

Oligodendrocyte (Support Cell)

Nerve Cell (Axon)

Schwann Cell (Support Cell)

Nerve Cell (Axon)

In PNS
Support cells

Oligodendrocyte Making Myelin

- oligodendrocyte
- axons
- node of Ranvier
- myelin
- myelin sheaths
Targets of neurotoxic compounds:

- The neuron
- The axon
- The myelinating cell
- The neurotransmitter system

The central nervous system (CNS) is protected from the adverse effects of many potential toxicants by an anatomic barrier between the blood and the brain, or a "blood-brain barrier."
BBB how it really works!

What I thought:

How it really works:

1. Capillary cell walls in body have large gaps. Allow even large molecules to pass into organ tissues.

2. Capillary cell walls in brain have small gaps. Allow only smallest molecules to pass into brain tissues.

Small molecules & atoms (oxygen, CO2, alcohol)

you learn something new every day
The security system for brain

The Blood Brain Barrier

Most capillaries in body

- Pore passage
- Lipid-soluble substances
- Transport mechanisms

Brain capillaries

- Carrier-mediated transport
- Transport mechanisms
- Lipid-soluble substances

Cell forming capillary wall

- Water-lined pore
- Astrocyte processes

Capillaries in cross section

- Tight junction (no pores)
What are the features that place the neuron at risk for the action of cellular toxicants?

- A high metabolic rate, neurons are highly dependent on aerobic metabolism because they must use this energy to maintain proper ion gradients. The brain is extremely sensitive to even brief interruptions in the supply of oxygen or glucose.
- A long cellular process that is supported by the cell body, single cell is not spherical, it is elongated and may extend over a meter in length. The length of neurons may exceed 200,000 times the dimensions of most other cells.
- An excitable membrane that is depolarized and repolarized rapidly.
Long cellular process
Types (Patterns) of neurotoxic injury

1. Neuronopathy: loss of the cell body and all its processes
2. Axonopathy: the axon may degenerate while the neuronal cell body continues to survive
3. Myelinopathy: either intramyelinc edema or demyelination.
4. Neurotransmission- Associated Toxicity
Types (Patterns) of neurotoxic injury
Nerve injury

NORMAL

WALLERIAN DEGENERATION

SEGMENTAL Demyelination

AXONAL DEGENERATION
Mechanisms of neurotoxicity: Neuronopathies:

- Certain toxicants are specific for neurons, resulting in their injury or death.
- Neuron loss is irreversible and includes degeneration of all of its cytoplasmic extensions, dendrites, and axons as well as the myelin ensheathing the axon.
Mechanisms of neurotoxicity:

Neuronopathies:
The initial injury to neurons is followed by apoptosis or necrosis, leading to permanent loss of the neuron.
## Compounds Associated with Neuronal Injury (Neuronopathies)

<table>
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<th>Neurotoxicant</th>
<th>Neurologic Findings</th>
</tr>
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<tbody>
<tr>
<td>Aluminum</td>
<td>Dementia, encephalopathy (humans), learning deficits</td>
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<tr>
<td>Arsenic</td>
<td>Encephalopathy (acute), peripheral neuropathy (chronic)</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Encephalopathy, delayed parkinsonism/dystonia</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>Encephalopathy (probably secondary to liver failure)</td>
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<td>Chloramphenicol</td>
<td>Optic neuritis, peripheral neuropathy</td>
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<td>Cyanide</td>
<td>Coma, convulsions, rapid death; delayed parkinsonism/dystonia</td>
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<td>Ethanol</td>
<td>Mental retardation, hearing deficits (prenatal exposure)</td>
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<tr>
<td>Doxorubicin</td>
<td>Insufficient data (humans); progressive ataxia (experimental animals)</td>
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<tr>
<td>1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)</td>
<td>Parkinsonism, dystonia (acute exposure)</td>
</tr>
<tr>
<td>Streptomycin (aminoglycosides)</td>
<td>Hearing loss</td>
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Doxorubicin (Adriamycin)

- In addition to its cardiac toxicity, Doxorubicin injures neurons in the PNS, by intercalating with DNA and interfering with transcription.
- Also generation of reactive oxygen species (ROS) by enzymatic electron reduction of doxorubicin by variety of oxidases, reductases, and dehydrogenases.
MPTP: (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)

- A contaminant formed accidentally during meperidine synthesis, MPTP produces over hours to days, the signs and symptoms of irreversible Parkinson's disease called Frozen addict syndrome (1982) in California, people who injected themselves with a meperidine derivative that was intended to serve as a substitute for heroin also received a contaminant MPTP.
- Although not identical, MPTP neurotoxicity and Parkinson's disease are extremely similar. Symptoms include masked faces, difficulties in initiating and terminating movements, resting "pill-rolling" tremors, rigidity, and bradykinesia.
Mechanism of Toxicity of MPTP

- MPTP itself is not toxic, it is lipophilic can cross BBB
- Autopsy studies have demonstrated marked degeneration of dopaminergic neurons in the substantia nigra, with degeneration continuing for many years after exposure.
- It appears that MPTP is metabolized to a pyridinium ion (MPP\(^+\)) by MAO-B enzyme, then enters the dopaminergic neurons of the substantia nigra, resulting in their deaths by blocking mitochondrial respiration at complex I.
- MPP\(^+\) acts as a general mitochondrial toxin.
MPTP-Mechanism of Toxicity
Mechanisms of neurotoxicity: Axonopathies (dying back neuropathy)

• The primary site of toxicity is the axon itself.
• The axon degenerates, and with it the myelin surrounding that axon; however, the neuron cell body remains intact.
• The toxicant results in a "chemical transection" (axotomy) cutting of the axon at some point along its length, and the axon distal to the transection degenerates, biologically separated from its cell body, degenerates in a Wallerian fashion.
Axonal degeneration

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Wallerian degeneration

The sequence of events that occur in the distal stump of an axon following transection is referred to as *Wallerian degeneration.*
Peripheral axons can regenerate, whereas central axons cannot (Why?)

- In the PNS, glial cells and macrophages support axonal regeneration.
- In the CNS, the release of inhibitory factors from damaged myelin and oligodendrocyte, astrocyte scarring actually interferes with regeneration.
- The clinical relevance of the disparity between the CNS and the PNS is that partial to complete recovery can occur after axonal degeneration in the PNS, whereas the same event is irreversible in the CNS.
Glove and stocking" neuropathy

• Axonopathies can be considered to result from a chemical transection of the axon.
• As the axons degenerate, sensations and motor strength are first impaired in the most distal extent of the axonal processes—the feet and hands—resulting in a "glove and stocking" neuropathy.
• With time and continued injury, the deficit progresses to involve more proximal areas of the body and the long axons of the spinal cord.
The most common neurologic effect of chronic arsenic intoxication is a sensory-predominant peripheral neuropathy in a "stocking-glove" pattern, as shown in the diagram to the right.
Diagram of axonopathies by axonal toxicants

[Diagram showing normal and affected neurons with axons and myelinating cells.]
Example: Carbon Disulfide (CS$_2$)

- Significant exposures of humans to CS$_2$ cause a distal axonopathy.
- Exposure of human occurs in the rubber and viscose rayon industries.
- Covalent cross-linking of neurofilaments occurs, and CS$_2$ is the ultimate toxicant.
- The clinical effects of exposure to CS$_2$ in the chronic setting is peripheral neuropathy with the development of sensory and motor symptoms occurring initially in a stocking-and-glove distribution. In addition to this chronic axonopathy, CS$_2$ can lead to aberrations in mood and signs of diffuse encephalopathic disease.
Sources of exposure to $\text{CS}_2$

- Viscose rayon industries
Organophosphorus compounds (NTE inhibitors):

- Apart from the insecticides, nerve agents, and some of the pharmaceuticals, OP compounds produced for other applications often have little or no anti-AChE activity.
- Some OP such as tri-ortho-cresyl phosphate (TOCP) causes a severe axonopathy without inducing cholinergic poisoning.
- These compounds are neuropathic and can cause a severe sensorimotor central, peripheral distal axonopathy called OP compound-induced delayed neurotoxicity (OPIDN) without inducing cholinergic poisoning. This condition is also referred to as a delayed neuropathy or delayed polyneuropathy.
Organophosphorus compounds

[Diagram showing the effects of organophosphorus compounds on acetylcholinesterase inhibition, leading to various clinical syndromes: acute cholinergic syndrome, intermediate syndrome, delayed polyneuropathy (OP/DN), and disability or death.]
Outbreaks of OPIDN

- In the United States, (1930) when Jamaica Ginger extract (Ginger Jake), a popular source of alcohol, was adulterated with TOCP.
- Another outbreak occurred in Morocco where olive oil was contaminated with TOCP.
Mechanism of Toxicity of TOCP

• When the principal target is neuropathy target esterase (neurotoxic esterase, NTE), OPIDN can result only if both inhibition of NTE occurs and the inhibited enzyme undergoes aging. Thus, inhibition alone is insufficient to precipitate toxicity.

• No aging .... No OPIDN
Mechanism of Toxicity of TOCP (cont.)

- The degeneration of axons does not commence immediately after acute organophosphorus ester exposure but is delayed for 7 to 10 days between the acute high-dose exposure and the clinical signs of axonopathy.
- The axonal lesion in the PNS appears to be repaired readily, and the peripheral nerve becomes refractory to degeneration after repeated doses. By contrast, axonal degeneration in the long tracks of the spinal cord is progressive.
Acrylamide

• Acrylamide is a vinyl monomer that is used in the manufacture of paper products, as a soil-stabilizing and waterproofing agent, and for making polyacrylamide gels in research laboratories.

• The neuropathy induced by acrylamide is a toxic distal axonopathy that begins with degeneration of the nerve terminal.

• Continued intoxication results in degeneration of the more proximal axon and abnormal axonal transport.
Pyridinethione (Pyrithione)

- Zinc pyridinethione has antibacterial and antifungal properties and is a component of shampoos that are effective in the treatment of seborrhea and dandruff.
- Only the pyridinethione moiety is absorbed after ingestion, with the majority of zinc eliminated in the feces.
Mechanism of axonopathy by pyridinethione

- Pyridinethione appears to interfere with the fast axonal transport systems, impairs the movement of rapidly transported vesicles, and slows the retrograde transport of vesicles.
- Any defects of the fast axonal transport systems contributes to the accumulation of tubular and vesicular structures in the distal axon.
- As these materials accumulate in one region of the axon, the axon degenerates in its more distal regions beyond the accumulated structures.
- The earliest signs are **diminished grip strength** and changes in the axon terminal, leading to a peripheral neuropathy.
Axonal transport system
Mechanisms of neurotoxicity: Myelinopathies

• Myelin provides electrical insulation of neuronal processes, and its absence leads to a slowing of conduction and irregular conduction of impulses between adjacent processes.

• Exposure to toxicants can result in either separation of the myelin lamellae, termed *intramyelinic edema*, or the selective loss of myelin, termed *demyelination*.

• Remyelination in the CNS occurs to only a limited extent after demyelination. However, Schwann cells in the PNS are capable of remyelinating the axon.
Mechanisms of neurotoxicity: Myelinopathies (cont.)

- Those toxic myelinopathies in which the disruption of myelin is diffuse generate a global neurological deficit, whereas those that are limited to the PNS produce the symptoms of peripheral neuropathy.
Toxicants results in Myelinopathies

- Amiodarone
- Hexachlorophene (Septisol)
- Lead
Toxicants results in Myelinopathies

- Amiodarone: cause Peripheral neuropathy by axonal degeneration and demyelination.
Hexachlorophene (Septisol):

- Caused neurotoxicity when newborn infants were bathed with the compound to avoid staphylococcal skin infections. After skin absorption of this hydrophobic compound, hexachlorophene enters the NS and results in intramyelinic edema, which leads to the formation of vacuoles, creating a "spongiosis" of the brain.
- Hexachlorophene causes intramyelinic edema that leads to segmental demyelination. Swelling of the brain causes increased intracranial pressure and axonal degeneration, along with degeneration of photoreceptors in the retina.
Toxicants results in Myelinopathies

Hexachlorophene (Septisol) (cont.)

- Humans exposed acutely to hexachlorophene may have generalized weakness, confusion, and seizures. Progression may occur to include coma and death.
Neurotransmission-Associated Neurotoxicity

- Nicotine
- Cocaine and Amphetamine
- Excitatory Amino Acids (EAA), “excitotoxins.”
Neurotransmission-Associated Neurotoxicity

Nicotine:

• It has diverse pharmacological actions and may be the source of considerable toxicity.

• These toxic effects range from acute poisoning to more chronic effects.

• Nicotine exerts its effects by binding to a subset of nicotinic cholinergic receptors.

• The rapid rise in circulating levels of nicotine after acute overdose leads to excessive stimulation of nicotinic receptors, a process that is followed rapidly by ganglionic paralysis.
Neurotransmission-Associated Neurotoxicity

- Initial nausea, rapid heart rate, and perspiration are followed by marked slowing of heart rate with a fall in blood pressure.
- Drowsiness and confusion may occur, followed by coma; if death results, it often results from paralysis of the muscles of respiration.
Neurotransmission-Associated Neurotoxicity

Cocaine and Amphetamines:
• The euphoric and addictive properties of cocaine derive from enhanced dopaminergic neurotransmission by the blocking of the dopamine reuptake transporter. Acute toxicity resulting from excessive intake, or overdose, may result in unanticipated deaths.

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Neurotransmission-Associated Neurotoxicity

- Like cocaine, amphetamines exert their effects in the CNS, altering catecholamine neurotransmission by competing for uptake via plasma membrane transporters and by disrupting the vesicular storage of dopamine.
- Amphetamines have been associated with an increased risk of abnormal fetal growth and development, cerebrovascular disease, and psychiatric and neurologic problems in chronic abusers.
Neurotransmission-Associated Neurotoxicity

Excitatory Amino Acids (EAA), “excitotoxins.” kainate, domoic acid, glutamate:

- Glutamate and certain other acidic amino acids are excitatory neurotransmitters in the CNS.
- The toxicity of glutamate can be blocked by certain glutamate antagonists, and the concept has emerged that the toxicity of excitatory amino acids may be related to conditions such as hypoxia, epilepsy, and neurodegenerative diseases.
Neurotransmission-Associated Neurotoxicity

- Glutamate is the main excitatory neurotransmitter in the brain, and its effects are mediated by several subtypes of receptors called excitatory amino acid receptors (EAARs). The two major subtypes of glutamate receptors are those which are:
  - Ionotropic receptors: Ligand-gated directly to ion channels; AMPA, NMDA, kainate.
  - Metabotropic receptors; coupled with G proteins
Glutamate, as an excitatory neurotransmitter, binds to its receptor and opens a calcium channel, leading to the excitation of the postsynaptic cell.
Mechanisms of excitotoxicity
Glutamate and Chinese restaurant syndrome

• The entry of glutamate into the CNS is regulated at the blood-brain barrier, and glutamate exerts its effects in the circumventricular organ of the brain, in which the blood-brain barrier is least developed.

• In this site of limited access, glutamate injures neurons, apparently by opening glutamate-dependent ion channels, ultimately leading to neuronal swelling and neuronal cell death. The only known related human condition is the "Chinese restaurant syndrome," in which the consumption of large amounts of monosodium glutamate as a food additives may lead to a burning sensation in the face, neck, and chest.
Chinese restaurant syndrome
(burning sensation in the face, neck, and chest)?
Chinese restaurant syndrome (food additives)
Sources of MSG:
Neurotransmission-Associated Neurotoxicity

**Kainate:**

- The cyclic glutamate analog kainate isolated from a seaweed in Japan is extremely potent as an excitotoxin, being a 100 fold more toxic than glutamate, and is selective at a molecular level for the kainate receptor.

- Like glutamate, kainate selectively injures dendrites and neurons and shows no substantial effect on the glia or axons. Injected into a region of the brain, kainate can destroy the neurons in that area without disrupting all the fibers that pass through that region.