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| **Toxic Responses of the Nervous System**  **Blood-Brain Barrier**  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." (Molecules must pass into the cell membranes of endothelial cells in the brain rather than between endothelial cells, as they do in other tissues). The blood-brain barrier also contains xenobiotic transporters that transport some xenobiotics that have diffused through endothelial cells back into the blood. The penetration of toxicants or their metabolites into the nervous system (NS) is related largely to their lipid solubility. The blood-brain barrier is incompletely developed at birth and even less developed in premature infants. This prompts a premature infant exposed to brain injury by toxicants more that later in life. |

**Energy Requirements**

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.

**Axonal Transport**

Impulses are conducted over great distances at rapid speed, providing information about the environment to the organism in a coordinated manner that allows an organized response to be carried out at a specific site. The transport of intracellular materials over great distances requires ATP.

**Axonal Degeneration**

After axotomy (cutting of an axon), there is degeneration of the distal nerve stump, referred to as *Wallerian degeneration,* which is followed by the generation of a microenvironment that is supportive of regeneration. After the axon dies, active proteolysis digestion occurs and only a myelin sheath surrounding a swollen degenerate axon remains, which then is digested by endogenous proteases. Schwann cells then provide physical guidance to direct the regrowth of a new axon and also release growth factors that stimulate growth. Resident macrophages and Schwann cells clear myelin debris so a new axon can grow into the space.

Degeneration of the distal axonal stump after transection is an active, matched process that can be delayed by decreasing temperature, preventing the entry of extracellular Ca2 + or inhibiting proteolysis.

**Myelin Formation and Maintenance**

Myelin is formed in the CNS by oligodendrocytes and in the peripheral nervous system (PNS) by Schwann cells

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| The maintenance of myelin is dependent on a number of membrane-associated proteins and on the metabolism of specific lipids present in myelin bilayers. Some toxic compounds interfere with this complex process of the maintenance of myelin and result in the toxic "myelinopathies". In general, the loss of myelin, with the preservation of axons, is referred to as *demyelination.*  **Neurotransmission**  Intercellular communication is achieved in the NS through the synapse. Neurotransmitters released from one axon act as the first messenger. Binding of the transmitter to the postsynaptic receptor is followed by modulation of an ion channel or activation of a second-messenger system, leading to changes in the responding cell. Various therapeutic drugs and toxic compounds affect the process of neurotransmission.  **Development of the Nervous System**  Replication, migration, differentiation, myelination, and synapse formation are the basic processes that underlie the development of the NS.  The immature NS is especially susceptible to certain agents. Ethanol exposure during pregnancy can result in abnormalities in the fetus, including abnormal neuronal migration and diffuse abnormalities in the development of neuronal processes. The clinical result of fetal alcohol exposure is often mental retardation, with malformations of the brain and delayed myelination of white matter. |

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| **Mechanisms of Neurotoxicity**  Individual neurotoxic compounds typically have one of four targets: the neuron, the axon, the myelinating cell, or the neurotransmitter system.  **Neuronopathies:**  When a neuronal cell body has been lethally injured, it degenerates, along with all its cellular processes. This process is a *neuronopathy* and is characterized by loss of the cell body and all its processes, with no potential for regeneration.  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 sheathing the axon.  Large number of compounds are known to result in toxic neuronopathies. The initial injury to neurons is followed by apoptosis or necrosis, leading to permanent loss of the neuron. These agents tend to be diffuse in their action, although they may show some selectivity in the degree of injury of different neuronal subpopulations. The expression of these cellular events is often a diffuse encephalopathy with global dysfunctions. |

**Doxorubicin**

Doxorubicin (Adriamycin) injures neurons in the PNS, by intercalating with DNA and interfering with transcription. The susceptibility of sensory and autonomic neurons appears to reflect the lack of protection of these neurons by a blood-tissue barrier within ganglia.

**Methyl Mercury**

The neurons that are most sensitive to the toxic effects of methyl mercury are those which reside in the dorsal root ganglia (not shielded by blood-tissue barriers). Methyl mercury exposure impairs glycolysis, nucleic acid biosynthesis, aerobic respiration, protein synthesis, neurotransmitter release and enhance oxidative injury and altered calcium homeostasis.

**Dopamine, 6-Hydroxydopamine, and Catecholamine Toxicity**

The oxidation of catecholamines by monoamine oxidase (MAO) yields H2O2, a known cytotoxic metabolite. The metal ion–catalyzed autoxidation of catecholamines, especially dopamine, results in the production of catecholamine-derived quinones as well as superoxide anion.

**Axonopathies**

When the injury is at the level of the axon, the axon may degenerate while the neuronal cell body continues to survive, a condition known as an "axonopathy.

A critical difference exists in the significance of axonal degeneration in the CNS compared with that in the PNS: Peripheral axons can regenerate, whereas central axons cannot. In the PNS, glial cells and macrophages support axonal regeneration. In the CNS, the release of inhibitory factors from damaged myelin and astrocyte scarring actually interferes with regeneration.

The number of axonal toxicants is large and is increasing in number. 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.

**Carbon Disulfide**

Significant exposures of humans to CS2 cause a distal axonopathy that is identical pathologically to that caused by hexane, with the development of sensory and motor symptoms occurring initially in a stocking-and-glove distribution. In addition to this chronic axonopathy, CS2 can lead to aberrations in mood and signs of diffuse encephalopathic disease.

**Acrylamide**

Acrylamide is a vinyl monomer that is used in many industries. 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.

**Organophosphorus Esters**

These compounds, which are used as pesticides and as additives in plastics and petroleum products, inhibit acetylcholinesterase and create a cholinergic excess. Which cause a severe axonopathy.

The degeneration of axons does not begin 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.

**Pyridinethione**

Zinc pyridinethione has antibacterial and antifungal properties and is a component of shampoos that are effective in the treatment of seborrhea and dandruff. Pyridinethione appears to interfere with the fast axonal transport systems, impairs the turnaround of rapidly transported vesicles, and slows the backward transport of vesicles. Aberration of the fast axonal transport systems most likely 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.

**Myelinopathies**

Myelin provides electrical insulation of neuronal processes, and its absence leads to a slowing of conduction and aberrant 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.

**Hexachlorophene**

It causes 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. Swelling of the brain causes increased intracranial pressure and axonal degeneration. Humans exposed acutely to hexachlorophene may have generalized weakness, confusion, and seizures. Progression may occur to include coma and death.

**Lead**

In young children, acute massive exposures to lead result in severe cerebral edema, perhaps from damage to endothelial cells. Chronic lead intoxication in adults results in peripheral neuropathy, gastritis, colicky abdominal pain, anemia, and the prominent deposition of lead in particular anatomic sites, creating lead lines in the gums and in the epiphyses of long bones in children. Lead in the peripheral nerve of humans slows nerve conduction.

**Neurotransmission-Associated Neurotoxicity**

A wide variety of naturally occurring toxins as well as synthetic drugs interact with intercellular communication through the process of neurotransmission. In terms of toxicity, most of the side effects of these drugs may be viewed as short-term interactions that are easily reversible. However, long-term use is associated with irreversible tardive dyskinesias or facial grimaces.

**Nicotine**

Nicotine exerts its effects by binding to a subset of nicotinic cholinergic receptors. Smoking and "pharmacologic" doses of nicotine accelerate heart rate, elevate blood pressure, and constrict blood vessels in the skin as a result of stimulation of the ganglionic sympathetic nervous system.

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

Exposure to lower levels for a longer duration, in contrast, is very common. The complications of smoking include cardiovascular disease, cancers, and chronic pulmonary disease. Chronic exposure to nicotine has effects on the developing fetus. Along with decreased birth weights, attention deficit disorders are more common in children whose mothers smoke cigarettes during pregnancy.

**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 unsuspected deaths.

Although cocaine increases maternal blood pressure during acute exposure in pregnant animals, the blood flow to the uterus actually diminishes. Depending on the level of the drug in the mother, the fetus may develop marked hypoxia.

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.

**Excitatory Amino Acids**

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.

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).

Development of permanent neurologic deficits occurred in individuals accidentally exposed to high doses of the EAAR agonist domoic acid, an analog of glutamate. The acute illness most commonly presented as gastrointestinal disturbance, severe headache, and short-term memory loss.