A Small Dose of Neurotoxicology

or

An Introduction to Toxicology of the Nervous System

What is neurotoxicity?

Voluntarily and involuntarily, we are exposed to a range of chemicals that affect the nervous system. We spend billions of dollars every year voluntarily purchasing chemicals such as caffeine, alcohol, and nicotine to influence our nervous system. Most stores and many industries are dependent on our desire to influence our nervous system. Many of us are familiar with the undesirable effects of too much caffeine or alcohol, which is a form of neurotoxicity. Fortunately, we quickly recover from the neurotoxic effects of caffeine or alcohol and from these experiences we learn to manage our consumption of these chemicals to minimize any undesirable effects and maximize the desirable effects. In this sense, many of us are experienced neurotoxicologists. Voluntary consumption of chemicals (drugs) that our society has classified as illegal is also common. These drugs range from the active ingredient of the easily cultivated marijuana plant to chemicals produced in illicit laboratories. The direct and indirect costs to our society of the "war on drugs" are enormous.

A range of legal drugs is sold by the pharmaceutical industry to treat illnesses of the nervous system. Advances in our understanding of the structure and function of the nervous system has accelerated the development of chemicals for treating diseases such as Parkinson's syndrome, Alzheimer's disease and mild depression. The treatment of mild depression with drugs like Prozac is a billion dollar industry. On the hand, some drugs may produce undesirable nervous system side effects that can limit their utility in disease treatment. The anticancer drugs vincristine and cisplatin damage sensory nerves in the fingers and the antibiotic, gentomycin can affect hearing. We are also involuntarily exposed to chemicals, compounds or even physical agents that can damage the nervous system. The science of neurotoxicology has largely focused on understanding the adverse effects of agents on the nervous system. This research has shown that the nervous system, particularly the developing nervous system, is vulnerable to permanent damage by a number of agents. For example, even low levels of lead exposure will permanently damage the nervous

system of young children, reducing their ability to learn and perform well in school, and ultimately affect their performance and **Neurotoxicity or a neurotoxic effect --** an adverse change in the chemistry, structure or function of the nervous system following exposure to a chemical or physical agent quality of life as adults. Alcohol, while having a predictable effect on the pregnant mother, can be disastrous for the nervous system of the developing infant. Many workers are exposed to agents such as solvents or pesticides that can transiently affect the nervous system or even cause permanent damage.

Physical agents such as noise and heat can also adversely affect the nervous system or degrade performance. Many people, including construction works that routinely use hearing protection devices a test to the awareness that excessive exposure to loud noise will permanently damage hearing. A more formal definition of neurotoxicity or a neurotoxic effect is as an adverse change in the chemistry, structure or function of the nervous system following exposure to a chemical or physical agent. An important part of this definition is that the effect may produce either structural change in the nervous system, such as gross cell loss, or function changes that may be related to subtle changes in nerve cell communication. Even minor changes in the structure or function of the nervous system may have profound consequences for neurological, behavioral, and related body functions. Often the very young and elderly are more susceptible to neurotoxic effects. Lead is a good example of a compound that at high levels of exposure can cause actual nerve cell damage but at low levels, particularly in children, can cause function losses such as decreased learning and memory.

Defining and testing for neurotoxicity is difficult because there is no one easy-to-define measure. Neurotoxicology effects can be divided into five areas (Table 15.1). Table 15.1 Neurological and Behavioral Effects of Exposure to Toxic Substances

1. Motor Effects: Convulsions, weakness, tremor, twitching,lack of coordination, unsteadiness,paralysis, reflex abnormalities, activity changes

2. Sensory Effects: Equilibrium changes, vision disorders, pain disorders, tactile disorders, auditory disorders

3. Cognitive Effects: Memory problems, confusion, speech, impairment, learning impairmen Mood and personality effects Sleep disturbances, excitability, depression,irritability, restlessness, nervousness, tension, delirium, hallucinations

4. General Effects: Loss of appetite, depression of neuronal, activity, narcosis stupor, fatigue, nerve damage

Case Studies

Caffeine:

Caffeine is the most widely consumed stimulant drug in the world. It occurs naturally in coffee, tea, and the cola nut and is added to many soft drinks. Many of us consume coffee and soda drinks because of the desirable stimulatory effects produced by caffeine; many of us have consumed too much caffeine and felt the consequences. The undesirable effects of caffeine, the agitation, the inability to concentrate, the mild tremors and the general unpleasantness, are a form of neurotoxicity. Literally your brain, and more specifically, the adenosine receptors in your brain, has too much caffeine. These effects are a reversible form of neurotoxicity. Fortunately, we metabolize caffeine quickly and the undesirable effects end. By experience we have learned how to moderate our caffeine consumption to avoid the unpleasant side effects. A great deal of money is made from the neuroactive and physiological effects of caffeine. You can learn more about this fascinating drug in the chapter on caffeine.

Lead:

The decision to use lead as a gasoline additive resulted in one of the greatest public healthdisasters of the twentieth century. Lead from the tail pipes of cars settled as dust over wide areas and was most prevalent in high traffic areas along city streets. Going from hand to mouth, the lead from cars and some additional lead from old lead-based paint were ingested by young children. In the 1970s and 1980s, researchers demonstrated that even low levels of lead exposure damaged the nervous system of children, confirming what the Greeks knew 2000 years ago: that "Lead makes the mind give way" (Dioscorides 2$_{nd}$ BC). Exposure of the developing nervous system to lead causes irreversible harm, degrading the learning and memory capabilities of the child and resulting in a lifetime of deficit. While lead was banned from most paint and removed from

gasoline, it still remains a threat to many children living in older homes with lead paint or near areas contaminated with lead. However, lead is still turning up in children's toys, jewelry, as a stabilizer in PVC plastics, and other products accessible to children. Lead is an example of a neurotoxic agent that causes permanent, irreversible damage to the developing nervous system, robbing a child of their genetic potential.

Prozac (fluoxetine hydrochloride):

Prozac, produced by the pharmaceutical company, Eli Lilly and Company, was first approved for the treatment of depression in Belgium in 1986. A year later, in 1987, it was approved for use in the United States. It is now approved for used in over 90 countries and used by more than 40 million people worldwide. Needless to say it is a very profitable drug. Prozac is commonly prescribed for treatment of mild depression, which is not uncommon as we make our way through the dramas and disappointments of life. Prozac, similar to many neuroactive chemicals, has a remarkably specific effect on one neurotransmitter. Typically, a neurotransmitter is released form one cell to communicate across a very small gap to be picked up by a neuroreceptor on another cell. Once the neurotransmitter has performed its function of communicating with the other it is either degraded or taken back up by the releasing cell to be reused. Prozac functions by blocking this reuptake, thus leaving more neurotransmitter within the cell gap to continue stimulating the receiving cell. Prozac selectively inhibits the reuptake of the neurotransmitter serotonin. The increased availability of serotonin appears to reduce the symptoms of depression. A range of drugs, including the well-known hallucinogen LSD, acts through serotonin.

MPTP and Parkinson's disease:

In the early 1980s, MPTP or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was accidentally produced as a contaminant of a new compound that clandestine chemists created in their search for a synthetic heroine. Tragically, drug users exposed to MPTP developed tremors and a lack of muscle control that was very similar to symptoms of Parkinson's disease. Parkinson's disease is usually a slow developing disease associated with the natural process of aging and the dying of cells in the brain. Further study revealed that MPTP attacked cells in a specific area of the brain that produce the neurotransmitter dopamine, the very same cells implicated in Parkinson's disease. This was the first time that a compound was clearly implicated in causing Parkinson's-like disease. Researchers immediately began searching for other compounds that

might cause Parkinson's disease or interact with the aging processes to accelerate the onset of the disease. A number of studies have examined the association of exposure to some pesticides with an increase in Parkinson's disease.

What Causes Neurotoxicity?

There is no simple or correct way to examine the causes of neurotoxicity. I have divided them into three overlapping areas: neurotransmitter / receptor effects, which are often transient; damage to the peripheral nerves, which is often permanent; and damage to the developing nervous system, which is almost always permanent. Nerve cells have unique structural and physiological features that often make them more susceptible to damage from chemical agents. Cells of the central nervous system have a high metabolic rate that makes them highly dependent on glucose and oxygen, much like computer chips need lots of electrical power. Anything that disrupts the flow of glucose or energy utilization within the cell causes a loss of function and potentially long-term damage.

Nerve cells, unlike muscle cells, can only work for a very short time without oxygen. The most obvious indicator of this is that we quickly loose consciousness when our brain is deprived of well oxygenated blood. Agents like carbon monoxide reduce the availability of oxygen to the brain resulting quickly in unconsciousness or even death. Cyanide, working by a very different mechanism, inhibits a cell's ability to utilize oxygen, which produces the same results. In the peripheral nervous system, the length of cells contributes to their increased susceptibility to damage from agents that disrupt the transfer of nutrients along the length of the cell. Acrylamide, for example, causes damage to the cell transport system, which results in paralysis that is first noticed in the legs. In the majority of cases, the cells of the nervous system cannot divide and replace themselves, thus most damage is permanent. The developing nervous system exposed to lead will be damaged for a lifetime. However, peripheral nerves can grow, recovering some of the connections and functionality that results in some sensation and return of movement, usually most noticeable in the arms and legs.

Neurotransmitter / receptor effects:

Many naturally occurring compounds and an increasing number of synthesized chemicals work by influencing the effectiveness of a specific neurotransmitter. Typically neurotransmitters

are released from one neuronal cell and are picked up by specific receptors in the adjacent cell, which causes the receiving cell to react. The receptor then releases the neurotransmitter into the gap between the cells. At this time the neurotransmitter must be removed either by being broken down by a specific enzyme or it can be taken back up by the releasing cell to be reused. A compound can influence a neurotransmitter and thus the response of the receiving cell several ways:

1. Blocking the receptor so that the neurotransmitter cannot reach the receptor and thus the receiving cell is unable to respond
2. Mimicking the neurotransmitter so that the receiving cell responds even though there is no naturally occurring neurotransmitter
3. Blocking the degradation of the neurotransmitter, thus leaving the neurotransmitter to react with another receptor
4. Blocking the reuptake of the neurotransmitter into the release cell, which leaves the neurotransmitter free to again react with the receptor.

Compound Neurotransmitter Action

1. Caffeine Blocks the adenosine receptor Stimulant

2. Organophosphate insecticides Increase the neurotransmitter acetylcholine by blocking its degradation

3. Nicotine Mimics acetylcholine, thus looks like increased acetylcholine

4. Fluoxetine Prozac Increases serotonin by blocking its reuptake into neuronal cells

5. LSD (lysergic acid diethylamide) Mimics serotonin, thus stimulating receptor

6. Hallucination THC - Delta 9 – tetrahydrocannabinol (Cannabis) Cannabinoid receptor Relaxation, euphoria, and enhancement of senses, increase in appetite, sense of time

7.Cocaine Blocks dopamine transporter, thus increasing dopaminergic stimulation Increases alterness & energy, euphoria, insomnia, restlessness, fear, paranoia,hallucinations

8. Domoic Acid (shell fish) Glutamate, aspartate Loss of memory

Very potent (poisonous) nerve gases permanently block the agent responsible for degrading acetylcholine thus causing death because the nervous system cannot recover.

Damage to the peripheral nerves:

The peripheral nerves of the body communicate sensation and deliver commands from the central nervous system to move muscles from our fingers to our toes – quite a distance. Peripheral nerves are wrapped by a specialized cell to form an insulation (myelin) that aids the transmission of electrical signal up along the length of the nerve cell. Agents damage the peripheral nervous system either by killing the nerve cell (neuronopathy), attacking the axon (axonopathy) or by attacking the insulation that surrounds the cells (myelinopathy).

Damage to the developing nervous system:

The developing nervous system is more vulnerable to damage than the mature nervous system for number of reasons. The blood-brain barrier of the central nervous system is not well developed in the very young, which allows toxic agents easy access to the nervous system. The nervous system develops through our gestation and continues changing well into our teens with cells multiplying, growing in size or length, migrating to a new location, or forming connections with other cells. During this period toxic agents may kill cells, interfere with their migration, or interfere with the cell-forming connections. Different areas of the nervous system develop at different times, so exposure to an agent such as alcohol during the fourth month of gestation will have different effects than exposure during the sixth month. Damage to the brain can range from the severe and obvious to the very subtle and undetectable. Exposure to high levels of alcohol during gestation can cause obvious reductions the ability of a child to perform well in school and even contribute to society.

More difficult to assess is the damage caused by very low levels of exposure. Low levels of exposure to alcohol or lead during development may reduce a child's IQ only slightly, by a degree that is within the normal range of variation. These more subtle changes can only be examined by comparing large groups of people, some of whom are exposed to the agent and some that are not. Group-based studies such as these were the first to show that even low levels of lead exposure during development can cause subtle decreases in IQ, thus depriving an individual of the ability to reach their full genetic potential. Any one individual would not know if their intellectual

capabilities had been reduced, but on a large scale these changes have serious implications for society.

Diseases of the nervous system:

Can toxic agents cause what have been classically defined as diseases of the nervous system, such as Parkinson's disease, Alzheimer's type dementia, multiple sclerosis, or amyotrophic lateral sclerosis (ALS) The discovery that the chemical MPTP can cause a syndrome very similar to Parkinson's disease really focused people's attention on the possibility that chemical agents may play a role in the onset of neurological disorders once exclusively associated with aging or just bad luck. MPTP selectively damaged the same neurons, in the same area of the brain, as those responsible for Parkinson's disease. Supporting the hypothesis that chemical agents may contribute to Parkinson's disease were data showing that incidence of this disease had increased when compared to historical patterns, which correlated with the increased use and exposure to chemicals. Additional research that the active metabolite of MPTP, that was really responsible for damaging the neurons, was very similar to the chemical structure of some pesticides.

Exposure to metals is associated with a number of neurological disorders. Researchers found that brain cells of many Alzheimer's patients has elevated levels of aluminum, and kidney dialysis patients could suffer from a neurological disorder related to elevated exposure to aluminum, but much additional study has never found that aluminum exposure cause Alzheimer's disease. Neurological and psychiatric disorders such as depression, hyperactivity, and manic depression have driven many pharmaceutical companies and research to develop neuroactive drugs to treat these conditions. This is an active area of research that will accelerate as we gain more knowledge of the underlying mechanisms of the nervous system. Early drugs used to treat psychiatric disorders often had highly undesirable side effects that often limited their long-term use or required additional drugs to manage the complications. Newer drugs are more specific and have fewer side effects.