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اسم المادة باللغة الإنكليزية: **General toxicology**

المرحلة: الرابعة

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عنوان المحاضرة باللغة العربية: السمية العصبية المرتبطة بالنواقل العصبية.

عنوان المحاضرة باللغة الإنكليزية:**Neurotransmission-Associated Neurotoxicity**

Neurotransmission-Associated Neurotoxicity

A wide variety of naturally occurring toxins, as well as synthetic chemicals, alter specific mechanisms of intercellular communication.

Although neurotransmitter-associated actions may be well understood for some agents, the specificity of the mechanisms should not be assumed. OP and carbamate pesticides produce their insecticidal actions by inhibiting AChE, the catalytic enzyme that ends the postsynaptic action of acetylcholine. The resultant cholinergic overstimulation produces signs of acute toxicity ranging from flu-like symptoms to gastrointestinal distress, ataxia, twitching, convulsions, coma, and death. These effects are not as well-correlated with AChE inhibition as might be expected for all such pesticides, leading to suggestions of additional mechanisms of actions that have since been verified in animal and in vitro studies.

Nicotine

Nicotine Widely available in tobacco products and in certain pesticides, nicotine 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 cholinergic receptors, the nicotinic receptors. These receptors are located in ganglia, at the neuromuscular junction, and also within the CNS, where the psychoactive and addictive properties most likely reside. Smoking and "pharmacological" doses of nicotine accelerate heart rate, elevate blood pressure, and constrict blood vessels within the skin. Because the majority of these effects may be prevented by the administration of α- and β-adrenergic blockade, these consequences may be viewed as the result of stimulation of the ganglionic sympathetic NS.

At the same time, nicotine leads to a sensation of "relaxation" and is associated with alterations of electroencephalographic (EEG) recordings in humans. These effects are probably related to the binding of nicotine with nicotinic receptors within the CNS, and the EEG changes may be blocked with mecamylamine, a nicotinic antagonist.

Acute overdose of nicotine has occurred in children who accidentally ingest tobacco products, in tobacco workers exposed to wet tobacco leaves, and in workers exposed to nicotine-containing pesticides. In each of these settings, the rapid rise in circulating levels of nicotine 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 is often the result of paralysis of the muscles of respiration.

Nicotine also places an increased burden on the heart through its acceleration of heart rate and blood pressure, suggesting that nicotine may play a role in the onset of myocardial ischemia. In addition, nicotine also inhibits apoptosis and may play a direct role in tumor promotion and tobacco-related cancers

Excitatory Amino Acids

Glutamate and certain other acidic amino acids are excitatory neurotransmitters. The discovery that these excitatory amino acids can be neurotoxic at concentrations that can be achieved in the brain has generated a great amount of interest in these "excitotoxins." In vitro systems have established that 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 such divergent conditions as hypoxia, epilepsy, and neurodegenerative diseases.

Glutamate is the main excitatory neurotransmitter of the brain, and its effects are mediated by several subtypes of receptors (Figure 1) called excitatory amino acid receptors (EAARs).

The two major subtypes of glutamate receptors are those that are ligand-gated directly to ion channels (ionotropic) and those that are coupled with G proteins (metabotropic). Ionotropic receptors may be further subdivided by their specificity for binding kainate, quisqualate, amino-3-hydroxy- 5-methylisoxazole-4-propionic acid (AMPA), and N-methyl-d- aspartate (NMDA). The entry of glutamate into the CNS is regulated at the blood–brain barrier. 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 consumption of large amounts of monosodium glutamate as a seasoning may lead to a burning sensation in the face, neck, and chest in sensitive individuals.

The cyclic glutamate analog kainate was initially isolated in Japan from seaweed as the active component of an herbal treatment of ascariasis. Kainate is extremely potent as an excitotoxin, being a hundredfold 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 glia or axons.

Cocaine and Amphetamines

Although nicotine is a legal and readily available addictive compound, cocaine and amphetamines are illegal, though still widely used. The number of adults using these drugs in the United States was approximately nine million in 1972. This number grew to near 33 million in 1982, and in the 2001 National Household Survey on Drug Abuse it was reported that just over 10% of those surveyed had ever used cocaine, while approximately 2.6% claimed to have used it in the last 12 months. Cocaine use is abundant in urban settings. It is estimated that from 10% to 45% of pregnant women take cocaine, and metabolites can be detected in up to 6% of newborns in suburban hospitals

Cocaine blocks the reuptake of dopamine (DA), norepinephrine, and serotonin at the nerve terminal in the CNS, and also causes release of DA from storage vesicles. The primary event responsible for the addictive properties and euphoric feeling when intoxicated is a

block on the DA reuptake transporter (DAT). This leads to enhanced DAergic transmission, and can result in a variety of symptoms in the user. Many individuals report a euphoric 753 feeling and increased self-confidence, in addition to racing thoughts and a feeling of pressure. In other users, a period of paranoid psychosis ensues. The mechanism of altered neurotransmission has been linked to the DA D1 receptor, as mice lacking this receptor fail to exhibit many of the same characteristic behaviors as wild- type mice.

Cocaine abuse also puts individuals at risk for cerebrovascular defects. Habitual users exhibit a greater degree of cerebral atrophy, compared by CT scan, and are more at risk of stroke and intracranial hemorrhage In chronic cocaine users, neurodegenerative disorders have been observed, similar to those observed with amphetamine use.

Amphetamines affect catecholamine neurotransmission in the CNS and have the potential to damage monoaminergic cells directly. Amphetamines, including methylenedioxymethamphet- amine (MDMA, or "ecstasy"), have become popular with young adults in recent decades due to the belief that it is a "safe" drug, and its ability to increase energy and sensation in adults. However, they also exert serious side effects. Similar to cocaine, the most pronounced effect of amphetamines is on the DAergic neurons, but they can also damage 5-HT axons and axon terminals. The result is a distal axotomy of DA and 5-HT neurons.

The exact mechanism of amphetamine neurotoxicity is still unknown, but several clues have emerged recently. It seems that oxidative stress plays a key role in toxicity. Following amphetamine-triggered DA release from the neuron, the DA is oxidized to produce free radicals. Chronic use can affect superoxide dismutase (SOD) and catalase balance in rodents, and amphetamine neurotoxicity is attenuated by antioxidants.

Asbestos

Toxic Responses of the Respiratory System

Asbestos refers to a group of silicate minerals in fiber form. The most commonly mind and commercially used asbestos fibers include the serpentine chrysotile asbestos and the amphiboles crocidolite, anthophyllite, amosite, actinolite, and tremolite asbestos. Exposure to asbestos fibers occurs in mining operations and in the construction and shipbuilding industries, where asbestos was at one time widely used for its insulating and fireproofing properties.

Asbestos causes three forms of lung disease: asbestosis, lung cancer, and malignant mesothelioma. Asbestosis is a form of pulmonary fibrosis with characteristically diffuse collagen foci and the presence of asbestos fibers, either free or coated with a proteinaceous material (asbestos bodies). Alveolar macrophage clearance is critical to the prevention of asbestosis and depends on fiber length, biopersistance, and dose. Lung cancer develops in workers in the asbestos mining industry and smoking of cigarettes greatly enhances risk. Malignant mesothelioma is a rare form of cancer that develops mainly in the pleural

mesothelium, the protective lining that covers the lungs, diaphragm, and interior of the chest wall. Unlike lung cancer, mesothelioma is not associated with smoking history.

In humans, amphibole fibers are implicated more often even when the predominant exposure is to chrysotile asbestos. Chrysotile breaks down much more readily than do the amphiboles.

Health hazards associated with asbestos exposure depend on fiber shape, length, and surface properties. Chrysolite asbestos are curved fibers and tend to be less toxic than crocidolite fibers that are long and thin, straight fibers. Fibers 2 μm in length may produce asbestosis; mesothelioma is associated with fibers ≥5 μm long, and lung cancer with fibers ≥10 μm. Fiber diameter is another critical feature. Fibers with diameters larger than ~3 μm do not readily penetrate into the peripheral lung. Only fibers ≥ 0.15 μm in diameter are likely to produce asbestosis or lung cancer. Mesothelioma, however, is more often associated with fiber diameter 0.5 μm because thinner fibers may be translocated from their site of deposition via the lymphatics to other organs, including the pleural surface.

The surface properties of asbestos fibers also contribute to toxicity. Crocidolite contains

more iron (including ferrous iron (Fe^{2}) that may participate in Fenton chemistry to generate reactive oxygen species) than chrysolite.

Once asbestos fibers have been deposited in the lung, they may become phagocytized by alveolar macrophages. Short fibers are completely ingested and subsequently removed via the mucociliary escalator. Longer fibers are incompletely ingested, and the macrophages become unable to leave the alveoli. Activated by the fibers, macrophages release mediators such as cytokine, chemokines, and growth factors, which in turn attract immunocompetent cells or stimulate collagen production. Asbestos- related lung disease

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thus may be mediated through the triggering of an epithelial injury and macrophage activation, and inflammatory events or through the production of changes that eventually lead to the initiation (DNA damage caused by reactive molecular species) or promotion (increased rate of cell turnover in the lung) of the carcinogenic process.

Silica

Inhaled particles of silicon dioxide (silica) cause a characteristic human lung disease—silicosis. Crystalline silica is a major component of the earth's crust; silicon is only second to oxygen as the most common element. Mineral forms of silicon exist primarily as crystalline SiO_2 with a central silicon atom forming a tetrahedron with four shared

oxygen atoms. The ubiquitous presence of silica has made it an occupational hazard ever since tools were cut from stone, and silicosis remains a significant industrial hazard

throughout the world in occupations such as mining and quarrying, sandblasting, and foundry work.

In addition to its structure, particle size, concentration, and surface properties affect the pathogenicity of silica both in vivo and in vitro. In humans, the most fibrogenic particle size appears to be about 1 μm (range 0.5–3 μm). In animal experiments (rats, hamsters), the comparable values appear to be 1 to 2 μm (range 0.5–5 μm). In animals, the concentration of silica dust is directly related to the intensity and rapidity of the histological reaction in the lung. When compared with stored silica or coated silica, freshly fractured silica particles produce more free radicals from their surface, increasing the respiratory burst when phagocytized and more pulmonary inflammation.

Silicosis may be acute or chronic with distinct pathological consequences. Acute silicosis occurs only in subjects exposed to a very high level silica (most often quartz or sand) small enough to be respirable (usually □ 5 μm) over a relatively short period, generally a few months or years. These patients have worsening dyspnea, fever, cough, and weight loss that can rapidly progress to respiratory failure, usually ending in death within two years. No known therapeutic strategy controls the relentless course of acute silicosis.

Chronic silicosis has a long latency period, usually □ 10 years and can be divided into simple and complicated silicosis. Even after radiographic changes, simple silicosis may be asymptomatic (ie, no dyspnea) with little change in pulmonary function. The x-ray presents fibrotic nodules, generally in the apical portion of lung. The hilar lymph nodes have peripheral calcifications known as egg- shell calcifications. Simple silicosis may progress into complicated silicosis, which is defined as the presence of conglomerate nodules larger than 1 cm in diameter. These nodules usually occur in the upper and mid- lung zones. In advanced stages, the nodules may be surrounded by emphysematous bullae. Chronic silicosis is associated with an increased incidence of tuberculosis.

The pathophysiological basis of pulmonary fibrosis in chronic silicosis is probably better understood than is the etiology of any other form of pulmonary fibrosis. The role of pulmonary alveolar macrophages in the ingestion of silica is an initiating event. Macrophages phagocytose silica particles into phagosomes that fuse with endosomes during the internalization process. In contrast to microorganisms, silica particles cannot

be degraded and macrophages undergo cell death, releasing these particles that are engulfed by other macrophages, thus perpetuating the process of phagocytosis and cell death.

Bleomycin

Bleomycin is a cancer chemotherapeutic drug with a major complication—pulmonary fibrosis that can be fatal. Bleomycin produces a sequence of injury and necrosis capillary endothelial cells, alveolar type I cell, edema formation and hemorrhage, delayed (after one–two weeks) proliferation and apoptosis of alveolar type II cells, and eventually thickening of the alveolar walls by fibrotic changes. In many tissues, the cytosolic enzyme bleomycin hydrolase inactivates bleomycin. In lung and skin, two target organs for bleomycin toxicity,

the activity of this enzyme is low compared with that in other organs. Bleomycin stimulates the production of collagen in the lung. Before increased collagen biosynthesis, steady-state levels of mRNA coding for fibronectin and procollagens are increased, subse- quent to a bleomycin-mediated release of cytokines such as TGFB1 and TNF.