Neurotoxicity: Introduction, causes, effects & Evaluation

Neurotoxicity

Toxicology of the Nervous System refers to situations in which an exposure to a chemical affects the function of

- **the nervous system**
- **or peripheral nerves**
- **(or neuromuscular junctions).**

They are mainly excitotoxins.

Toxic substances may act on membrane proteins (receptors, channels, transporters, enzymes etc.).

Naturally occurring toxic substances such as tetrodotoxin (from the puffer fish) and saxitoxin (from the marine alga responsible for paralytic shellfish poisoning) block ion channels, initially is followed by difficulty in speaking and swallowing and by an inability to coordinate muscular movements. In severe cases, respiratory paralysis may result.

Neurotransmitters and Chemical Synapse

The normal chemical synapse functions in the following fashion:

- Neurotransmitters (the most important one at neuromuscular junctions being acetylcholine) are secreted from presynaptic neurons.

- The transmitters normally bind to the ion, especially sodium, channels of postsynaptic membranes.

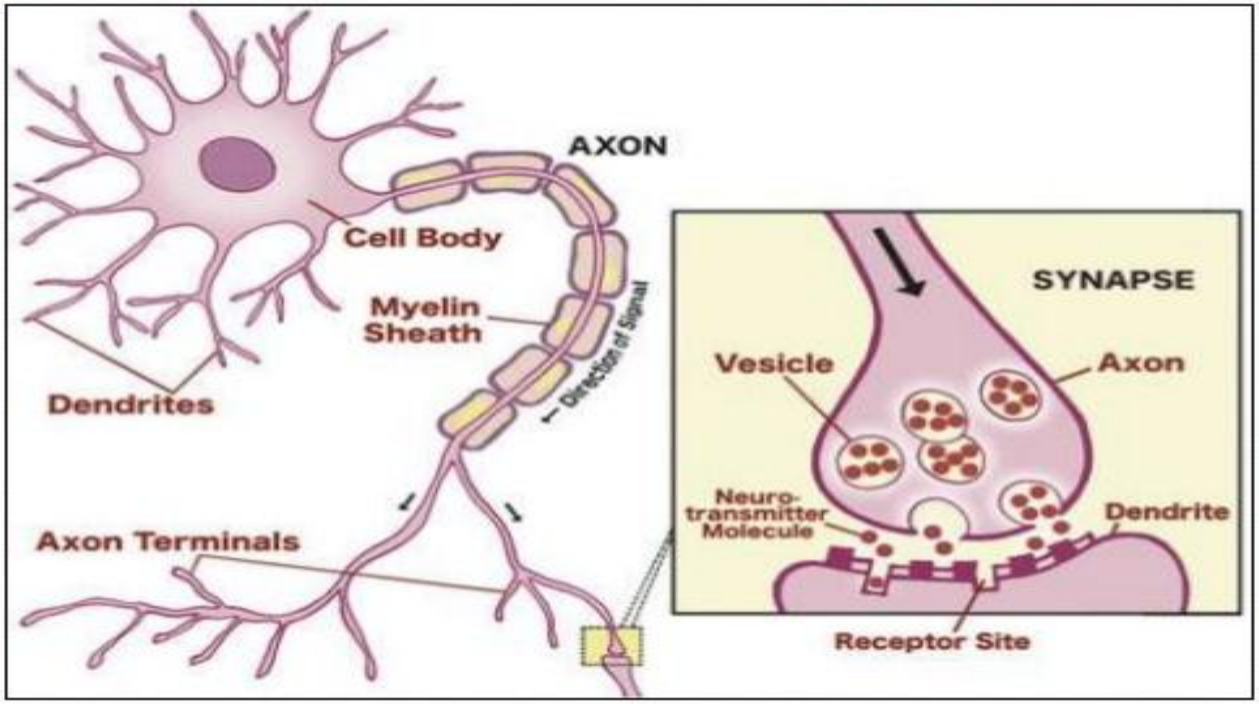
- **The binding causes the opening of the sodium channel and consecutive depolarization.**
- **This causes the postsynaptic cell to become excited.**
- **The excitation of the postsynaptic cell is finished when the neurotransmitter is enzymatically broken down, which results in the closure of the sodium channel.**
- **The most important neurotransmitter in neuromuscular junctions is acetylcholine, which is broken down in an acetylcholinesterase-catalyzed reaction.**
- **Chloride currents via GABAergic (GABA = γ-aminobutyric acid) channels oppose the excitation.**

Neurotoxicity :

Any **adverse change** in the structure or function of the nervous system during development or at maturity following exposure to a chemical, physical, or biological agent

"You cannot reach your full genetic potential with a damaged nervous system."

- S.G. Gilbert



Structure : Neuron

Nervous System parts

Central Nervous System (CNS) : Brain and Spinal cord, glial cells

Peripheral Nervous system (PNS) : Nerves, bundles of the axons, glial cells
- connect the CNS to every other part of the body

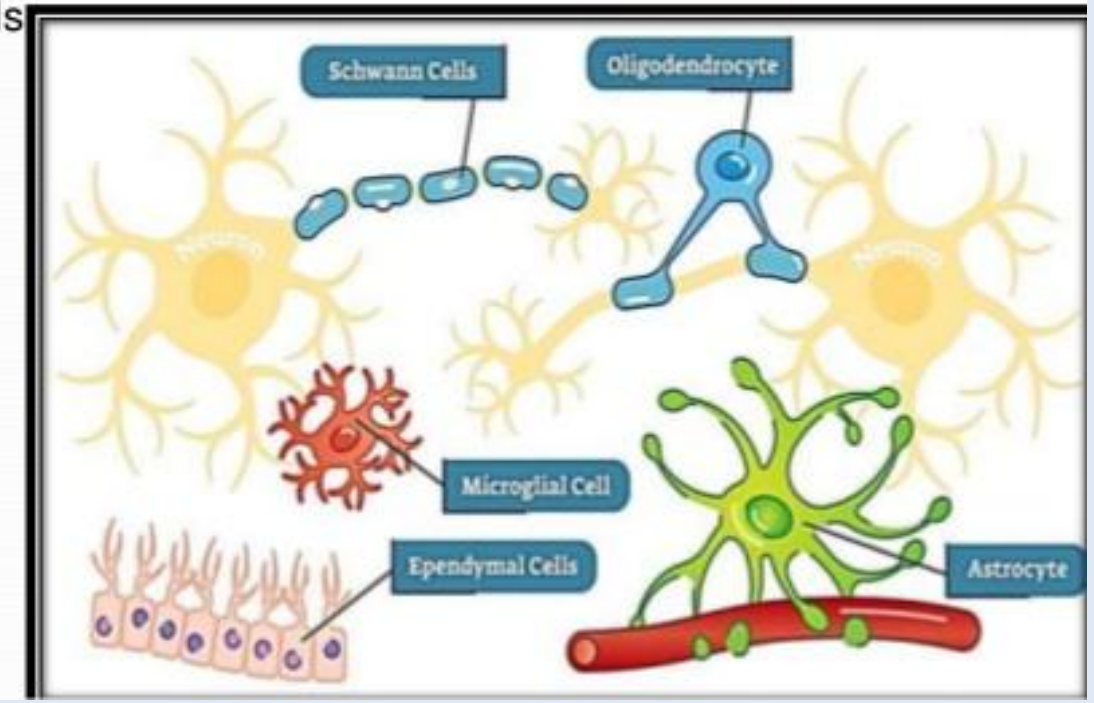
Glial cells

CNS - Oligodendrocytes, Astrocytes, Ependymal cells and microglia.

PNS - Schwann and satellite cells

Function -

- Removal of dead neurons
- Fight pathogens
- Structural integrity
- Insulation
- Supply of nutrients and oxygen
- Neurotransmission



POSSIBLE INFLUENCES OF NEUROTOXICANTS ON THE CHEMICAL SYNAPSE.

When the synapse is functioning normally, neurotransmitter (e.g. acetylcholine; red circles) is liberated in the synaptic cleft, and binds to the postsynaptic ion channels, affecting their activity.

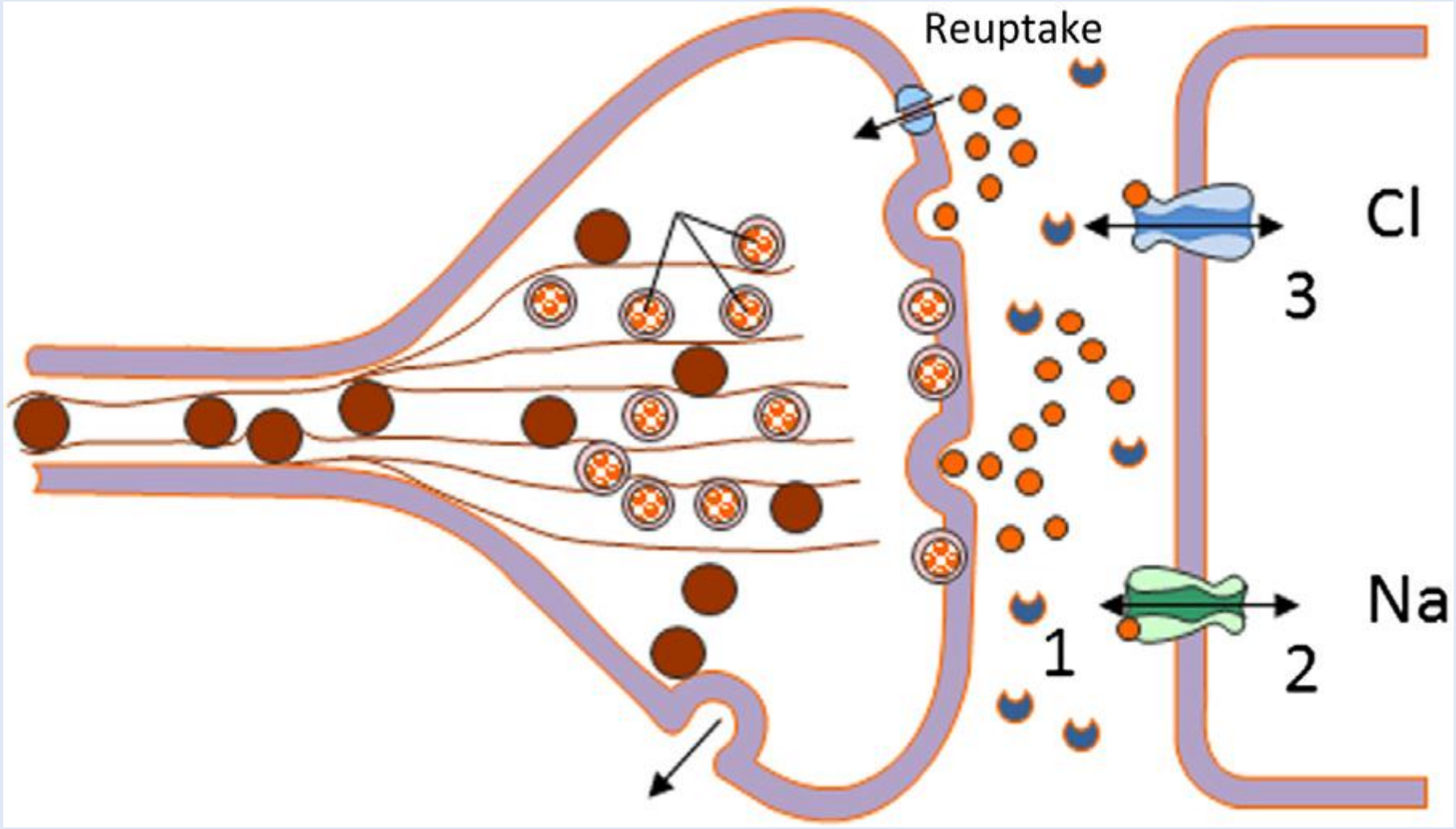
Normally, the transport of chloride and/or sodium is affected in such a way that the postsynaptic cell is depolarized, whereby it is electrically activated.

The synaptic function is stopped when the neurotransmitter concentration decreases in the synaptic cleft either by reuptake or by enzymatic breakdown.

EXCITOTOXINS

As a result, the ion channel activity returns to a normal level.

Many toxicants are excitotoxicants that prevent the return of the postsynaptic cell to the resting state.


Reuptake
Cl
3
Na
1
2

1. Organophosphate

organophosphate insecticides inhibit acetylcholine breakdown by inhibiting acetylcholinesterase activity.

2. Pyrethroids and DDT target sodium channels preventing their proper closure.

3. Dieldrin and lindane facilitate excitation by decreasing GABAergic chloride flow.

It is important to note here that, although they are called insecticides, the compounds will affect all animals with similar chemical synapses.

The toxicity to a given animal type depends on the

- uptake and metabolism of the toxicant,
- affinity of the site of action of the chemical in the particular animal.
- Every once in a while, insecticides are much more toxic to nontarget aquatic animals than to the target terrestrial insects.

SEDATIVES

Another group of neurotoxins is sedatives, with benzodiazepines as the most important group.

These compounds are aromatic, and may cause their actions by influencing the fluidity of neural membranes.

Thus, the majority of narcotic compounds affect cells in a fashion similar to ethanol, being membrane toxicants.

Selective Serotonin Uptake Inhibitors (SSRIs)

Another group of neurotoxins that has recently become an issue in the aquatic environment is antidepressants, especially the selective serotonin uptake inhibitors (SSRIs) such as **fluoxetine.**

Mode of Action of SSRIs:

The mode of action of the SSRI compounds is considered to be the following:

- They increase the serotonin (5-HT) level of synapses by inhibiting serotonin transporters.

- serotonin reuptake occurs by cells, causing long-lasting elevation of the synaptic serotonin level.
- To have antidepressant effects, the plasma concentration in patients needs to be normally more than 50 µg/l.
- The neural mode of action has been accepted as the major effect.

EFFECT OF NEUROTOXICITY ON AQUATIC ANIMALS

Reported effects in aquatic invertebrates are often in reproductive behavior or reproduction, e.g. induction of spawning, directly.

- Some reports suggest that these effects take place at presently observed environmental concentrations, which can be a few ng/l.
- Even with some bioaccumulation occurring, this is much below the concentration required for neural effects in mammals.
- If this is found to be a more common situation, then it is possible that a new effect pathway, independent of the traditional mammalian neural one, has been found.

Neurotoxicity Risk Assessment

- Risk characterization is the qualitative and quantitative estimation of the severity and probability of occurrence of known and potential adverse effects of a substance in a given population

- Hazard characterization -

- **Structural endpoints** : Changes in morphology
- **Neurophysiological endpoints** : Alterations in synthesis, release, uptake, degradation of neurotransmitters
- **Neurochemical endpoints** : Change in velocity, amplitude, or refractory period of nerve conduction
- **Behavioral endpoints** : Changes in touch, sight, sound, taste, or smell sensations
- **Epidemiologic studies** : Distributions and determinants of disease human populations

❑ **Dose response analysis**

- Determination of The lowest-observed-adverse-effect level (**LOAEL**)
- Determination The no-observed-adverse-effect-level (**NOAEL**)
- Determination Benchmark Dose

❑ **Exposure Assessment**

Exposure assessment describes the magnitude, duration, frequency, and routes of exposure to the agent of interest