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TOXICITY IN MOLECULES: ANALYSING THE KEY PARAMETERS IN DETERMINING THE POISON LEVELS TO DEVELOP AN ANALYSIS METRICS

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ABSTRACT

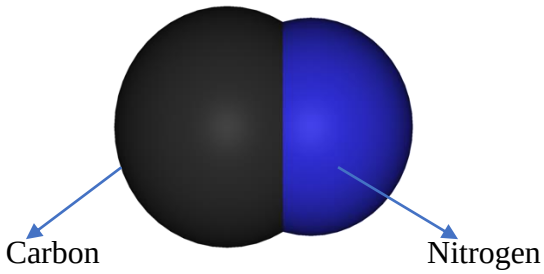
The study of toxicity in a molecule has become a common theme of research nowadays. Molecules are said to be poisonous if they interfere with the body's chemistry and alter it in such a way that leads to a rather unconventional mode of the human biological mechanism.

Therefore, a poison can be defined in several ways and the three most important things which determine whether a chemical can be described as poison are (1) its effect on the human body, (2) its speed of action in the body, (3) the effect it has in small doses. It is not specifically true for poison to show severe negative effects in high doses.Some poisons are really strong and effective so less of it is required to cause death. Whereas for weak poisons, you need more of it to kill someone. Therefore, the potency of poison decides what effects it will show and how quicklythe symptoms will unfold.

Poisons have different structures and functions and they exhibit distinct properties when they come into contact with human cells. Some poisons aim for the digestive system, some for the nervous system, and this all varies with the affinity of the poison molecule with a specific section of our body. In short, some poisons exploit the sensitivity of receptors on the target cells and affect the components of the cells required to complete processes essential for human life. Therefore, I have chosen three poisons to explain my ideas in detail, all of which result in different symptoms due to a meeting of poisonous molecular structures with the delicate receptor molecules.

Keywords: *Doses; Effect; Toxicity; Protein; Blockage; Mechanism; Receptors; Structures*

Some poisons, such as cyanide, function as inhibitory molecules. Their job is to interrupt a course of action and decrease its activity. The cyanidemolecule's basic structure involves the grouping of carbon and nitrogen atoms with a strong triple covalent bond (C≡N). The bond means they share between them three pairs of electrons. High bond energy is what causes cyanide to be inseparable from the biological compounds in the body it binds to. More importantly, the exchange of electrons is impeded by the toxic molecule because its ability to bind to an iron ion in the enzymes that catalyse the respiration process effectuates the rapid drop-off in oxygen levels inside the body.



Energy production process is a very convoluted and a hierarchal process which takes place inside the mitochondria. Additionally, several coenzymes, small non-protein organic molecules, aid in this activity by helping enzymes catalyse a chemical reaction. Coenzymes, such as NADH, actively take part in the cellular respiration. The role of NADH is to oxidise (lose electrons) and reduce (gain electrons) to set up an electron transport chain. A series of oxidation and reduction reactions cause a constant exchange of electrons among the electron donors and receptors respectively.[1]

Oxidation

$$NADH \longrightarrow NAD^{+} + H^{+} + 2e^{-}$$

Then these two electrons bind to an electron receptor called Cytochrome C. The role of Cytochrome C is to transfer these lost electrons to Oxygen so that it gets reduced.

Reduction

$$2e^{-} + 2H^{-} + \tfrac{1}{2}\, 0_2 \longrightarrow H_2O$$

Intriguingly, the iron atom is involved in the electron exchange procedure. When two electrons are lost due to NADH's oxidation, they tie with the iron ion as a result of electrostatic attraction between oppositely charged particles, and this is the moment when cyanide showcases its toxic properties. When cyanide is ingested or inhaled, it gets broken down into cyanide ionsand gets diffused into the blood. Eventually, it strongly binds to the iron ion so much so that it is almost impossible to separate them. Formation of π-bonds[2] causes two p-orbitals from iron and cyanide ions to overlap on either side. The bond energy naturally increases as there are more electrons involved in the bond. Therefore, it attaches to iron more strongly than oxygen does.

Theoretically, energy from electron transport chains is released which pumps the hydrogen protons, and this gradient leads to the diffusion of protons through ATP synthase resulting in the production of ATP (energy providing molecule).[3] In the case of cyanide, electron transfer to oxygen becomes diminished, hydrogen proton pumps get reduced, and a stronger gradient for protons is required to

[1] https://www.khanacademy.org/science/biology/cellular-respiration-and-fermentation/oxidative-phosphorylation/v/oxidative-phosphorylation-and-the-electon-transport-chain

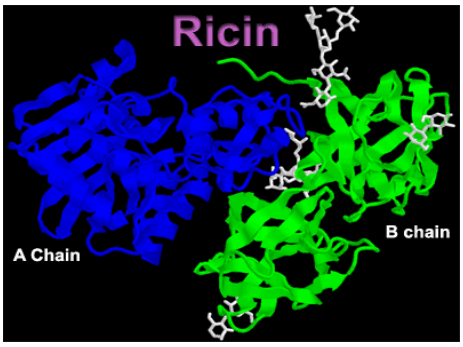
[2] John Emsley - "Molecules of Murder" Royal Society of Chemistry (23 Jun. 2017)chapter 8 'Cyanide and the Death on the Nile', 8.2- The Chemistry of Cyanide Pg-156-157ISBN 978-1-78262-474-5

[3] ISBN 978-0-19-835192-4 "A Level Biology for OCR" Chapter 18.4- Oxidative phosphorylation.

be overcome. Eventually, the protein is rendered inactive by cyanide and other biochemical processes in our body don't progress any further. All the oxygen in our body due to continuous breathing is left useless, and that is why one notices that a cyanide victim becomes very red because red unreacted oxygenated blood is flowing in the person's veins.[4]

One can become exposed to cyanide in some ways: inhalation, injection and injection. Therefore, the speed of reaction varies slightly because it enters through different areas of the body. Breathing air with 300 ppm for 30 minutes can prove to be highly fatal. Ingestion of cyanide in the form of a compound, for example, HCN, 3 mg/Kg body weight can kill someone within three days. So, for an average 70 Kg person, 210 mg of cyanide will utterly destroy the body.[5]

Ricin is one more of those inhibitory molecules which affect the protein synthesis. Ricin itself is a protein, and this acts as a bonus for the molecule to invade the human cell and cause havoc – cells become protein-deficient.



The molecule is composed of two polypeptide chains (multiple layering of amino acids): chain A and chain B. As the molecule enters the blood system, it binds to the cell membrane. The role of chain B comes into play; its glycoprotein binding sites dock on the plasma membrane which allows the molecule to enter the cell[6]. As soon as the molecule gets into the cell, the toxin starts getting produced by the chain A. During the toxin synthesis, the human cell is well aware of an inappropriate series of events and it does respond to it by breaking the molecule down using enzymes inside the lysosomes. Nonetheless, the toxin manages to escape the attack and reach the Golgi apparatus, the post office of the cell. From there, the toxin gets transported to Rough Endoplasmic Reticulum, the factory of any cell, for processing[7]. Here, ricin A chain splits from the ricin B chain and the former makes its way through the nucleolus towards the most exciting part of its mechanism.

[4]"Molecules of Murder by John Emsley"Royal Society of Chemistry (23 Jun. 2017)chapter 8 'Cyanide and the Death on the Nile', 8.4- Toxicity of Cyanide, and its antidotes. Pg-160-161ISBN 978-1-78262-474-5

[5]"Molecules of Murder by John Emsley"Royal Society of Chemistry (23 Jun. 2017) chapter 8 'Cyanide and the Death on the Nile', 8.4- Toxicity of Cyanide, and its antidotes. Pg-160-161

[6]Walsh MJ, Dodd JE, Hautbergue GM. Ribosome-inactivating proteins: Potent poisons and molecular tools. *Virulence*. 2013;4(8):774-784. doi:10.4161/viru.26399. (Introduction)

[7] http://pdb101.rcsb.org/motm/161

Ricin A binds to the ribosomes, which are the protein's synthesis stations in the cell. The job of a ribosome is to mate two amino acid bases together to form a polypeptide chain; however, ricin A chain obstructs this process. Initially, mRNA replicates the gene code in order to be taken to the ribosomes for protein synthesis. A set of bases join together in a line on mRNA for the complementary bases on tRNA to link with the amino acids. The bases keep attaching to their matching fragment, and the amino acid keeps forming a peptide bond with the former amino acid. This formation keeps occurring unless an external entity, like ricin, disrupts the action. In effect, the ricin A chain binds to the 28s rRNA (fundamental structural element of ribosomes) in the larger Ribosomal subunit[8] and removes an adenine base from the mRNA which means the protein elongation factor is no longer able to bind. This prevents a long polypeptide chain of amino acids from forming and leads to cell death. Consequently, several cells fail to make essential proteins for different parts of the body; many organs such as the liver, spleen and kidneys do not get the structural support, and they stop operating.

A single ricin A chain can inhibit 1500 ribosomes per minute[9]. It tends to be extremely potent because the toxin removes the adenine base from every triplet of codon on the mRNA. There are thousands of ribosomes performing the same job, and once chain A inactivates one ribosome, it binds to another one. Owing to that reason, 0.1 micrograms/Kg is sufficient to cause the damage. Therefore, for a healthy 70 Kg man, 7 micrograms would pose a severe threat to his life.[10]

Some poisons tend to have affinity with the receptors in the nervous system, which causes them to bind to specific channels. A change in natural neuromodulation causes interrupted nerve impulses around the body and it leads to severe problems. One of those poisons is Strychnine, which is an organic neurotoxin ($C_{21}H_{22}N_2O_2$) and originates from the Philippines. It is generally found in the nuts of the tree *Strychnos nux-vomica*. The toxin is extracted and used by farmers to exterminate pests; however, it has also been used as a homicidal agent. Crucially, strychnine attacks the nervous system by meddling in the critical ion exchange between two neurons by acting as a barrier.

For the information to proceed, in the form of an action potential, the acetylcholine (neurotransmitter) has to be released by the pre-synaptic membrane and be accepted by the post-synaptic membrane. Change in voltage in the membrane causes some ion gated channels to open up and allow the influx of ions such as calcium (Ca^{2+}), sodium (Na^+), potassium (K^+) and chlorine (Cl^-). The voltage, theoretically, decides whether the potential is strong enough to flow or not. If a positive ion is entering, then it reduces the threshold voltage (minimum voltage required for an action potential to flow), and the membrane is said to be hypopolarised. If a negative ion flows in, then it increases the threshold voltage, and thus, it makes the membrane hyperpolarised. As the voltage-gated channels on the sides of the neuron open up, Ca^{2+} rushes through the membrane and triggers the release of acetylcholine. Once it leaves the pre-synaptic membrane, it docks on ligand-

[8]Walsh MJ, Dodd JE, Hautbergue GM. Ribosome-inactivating proteins: Potent poisons and molecular tools. *Virulence*. 2013;4(8):774-784. doi:10.4161/viru.26399.

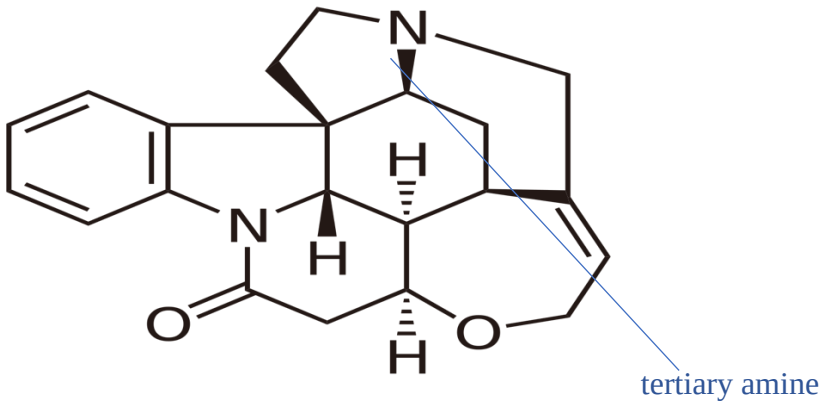
[9] http://pdb101.rcsb.org/motm/161

[10]ISBN 978-1-78262-474-5 "Molecules of Murder" chapter 1 'Ricin and the rolled Umbrella', 1.2- Toxicology and Chemistry Pg-4

gated sodium channels and changes their shape to allow the inflow of Na^+ ions. The process pretty much continues, i.e., Na^+ ions enter the new membrane, open up the voltage-gated channels and start the propagation of next action potential in the post-synaptic membrane.

For the action potential to stop, the acetylcholine has to be contained within the pre-synaptic membrane. Now here comes the role of Chloride ions (Cl^-). As the Acetylcholine, released from Inhibitory membrane, attaches to a different ligand-gated channel, it changes the shape in such a way that only Cl^- ions are tolerated. The Influx of these ions, then, hyperpolarises the post-synaptic membrane from, say, -90meV to -110meV. In order for this to be equalised, more Na^+ must be required and this can only happen when more acetylcholine docks at Sodium channels. Due to reduced availability of acetylcholine, less Sodium enters the membrane. Therefore, the impulse is stopped and the action potential doesn't go through.

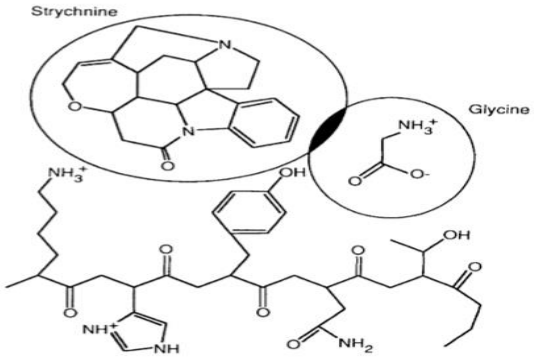
In the case of Strychnine, Cl^- allows the release of a special inhibitory molecule – glycine. It specifically binds to glycine receptor and deactivates the action potential. It antagonises the effect of glycine which produces a postsynaptic inhibitory potential (hyperpolarization) via an increase in chloride conduction. Under normal circumstances, glycine binding to the channel causes increased inward flow of Cl^-, hyperpolarizing the cell and inhibiting its ability to propagate nerve signals[11]. The inhibitory postsynaptic potential appears to result from an increase in chloride conductance. Strychnine prevents the uptake of glycine at inhibitory synapses, especially in the ventral horns of the spinal cord. When it enters the body (ingestion), it reaches the gut and gets absorbed into the blood very easily due to the presence of the basic amine. The strychnine molecule enters as a charged molecule, and with a weak amine base, it gets easily dissociated and diffused into the bloodstream.



After diffusion, it enters the nervous system and blocks the release of inhibitory post-synaptic potential in the motor neuron. When glycine is released from the pre-synaptic membrane, strychnine intervenes between glycine and its receptor by acting as a spatial blockage.[12]

[11]https:/calpoison.org/news/strychnine-poisoning

[12]'Handbook of Membrane channels: Molecular and Cellular Physiology by Robert Vandenberg and Peter Schofield' Academic Press Inc (Sept. 1994)Chapter 21- Inhibitory Glycine and $GABA_A$ receptors Pg. 327-328.ISBN 978-0125506403



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Strychnine bonds noncovalently[14] to the lysine and tyrosine residues[15], and this does not allow glycine to interact with the receptor molecule fully. The bond (disulfide bridges) plays a very important role in the ligand recognition. So, if the appropriate molecules do not contact with the receptor in the desired way, the ligand gates do not open. Consequently, the ion exchange becomes very restrained; EPSPs increase suddenly and the post-synaptic membrane becomes hypopolarised to, say, -70meV. As it is very close to the threshold voltage, that is -60meV, less acetylcholine is required to trigger the action potential, and thus, less Na^+ need to enter through sodium channels. Therefore, the 'jumpiness' keeps passing on; it never stops. As a result of this, the body becomes short of oxygen because of demands being made by muscle contractions and the victim eventually dies of asphyxia.

The chances of getting exposed to strychnine are very minimal, and however if someone does ingest it, he could be in real danger. 0.2mg/Kg weight of a person can prove to be fatal; therefore, for an average 70 Kg person 35 mg would kill him[16]. The victim goes through a series of attacks, and they all vary owing to the dose intake. If one takes a high dose, an individual will not last 10 minutes and if a lesser dose is taken, it could last for 3 hours. However, a lesser dose is more painful because as the victim experiences intermittent attacks for a more extended period.

To conclude, we are exposed to many poisonous molecules some of which have the same feature in common, that is, they disrupt the conventional human biological functioning by attacking the sensitive receptors in the cell. I have explained the mechanism of some of the poisons which have similarities but their target areas are very different from each other. By and large, it all comes down to the administration of the poison inside the body and the effect it has on the vital intra-cellular processes which provide a backbone to the sustenance of human life.

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[14]https://en.wikipedia.org/wiki/Strychnine, 'Mechanism of action'

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[16] http://www.chm.bris.ac.uk/webprojects2006/Greeves/Symptoms.html

BIBLIOGRAPHY

- https://www.khanacademy.org/science/biology/cellular-respiration-and-fermentation/oxidative-phosphorylation/v/oxidative-phosphorylation-and-the-electon-transport-chain
- "Molecules of Murder" chapter 8 'Cyanide and the Death on the Nile', 8.2- The Chemistry of Cyanide Pg-156-157
- "A Level Biology for OCR" Chapter 18.4- Oxidative phosphorylation.
- "Molecules of Murder", John Emsley,Royal Society of Chemistry (23 Jun. 2017)
- Walsh MJ, Dodd JE, Hautbergue GM. Ribosome-inactivating proteins: Potent poisons and molecular tools. *Virulence*. 2013;4(8):774-784. doi:10.4161/viru.26399. (Introduction)
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- https://en.wikipedia.org/wiki/Strychnine, 'Mechanism of action'
- http://www.chm.bris.ac.uk/webprojects2006/Greeves/Symptoms.html