CHAPTER 13

Toxicokinetics and Toxicodynamics: Understanding how Toxins Interact with the Body

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SUMMARY

Humans interact with a wide range of environmental toxicants through different pathways. The concepts of toxicodynamic and toxicokinetic elucidate the penetration of various toxicants in the body through various routes particularly dermal, inhalation, and ingestion and their interaction with living systems. Toxicokinetic(s) elaborates on the dosage, time duration and route of penetration of different xenobiotics as well as environmental toxicants while the term toxicodynamic explain the dynamic interactions of these xenobiotics and toxicants with different body organs. Different toxicants including mercury, lead, arsenic, paraquat and perfluoroalkyl substances activate various signaling pathways which exert different impacts on body organs. This chapter will elucidate how a drug or toxicant enters the body and interacts with various organs.

INTRODUCTION

Toxicokinetics is a pivotal component in evaluating the risks associated with different xenobiotics (Dixit et al., 2003). The interdisciplinary area of toxicokinetics (TK) combines the theories and practices of toxicology and pharmacokinetics. It is essential for interpreting the properties of absorption, distribution, metabolism, excretion, and toxicity (ADMET) of xenobiotic in models including people and animals, considering different exposure routes, dosages, and frequencies (Yu & Li, 2017). TK data are a crucial component of the extrapolations required in those frameworks, including interspecies extrapolation, route-to-route extrapolation, and mechanistic considerations (Coecke et al., 2013).

The dynamic interactions of a harmful phytochemical or toxin with biological targets and their corresponding physiological reactions are known as toxicodynamics. Based on its structural and chemical makeup, a phytochemical toxicant that enters the body causes a reaction by binding proteins or interacting with receptors. When compared to larger levels, a toxicity of substances in a particular organism will be less or nonexistent at lower doses. Without it, life could not survive because it is always up against chemical difficulties, whether they come from manmade or natural components. Therefore, it should come as no surprise that all living things devote a sizable portion of their biochemistry to the metabolism, excretion, and inactivation of toxic compounds that come from both endogenous and external sources (Monosson, 2012).

TOXICOKINETICS

Absorption of different xenobiotics/toxins

Toxicants enter the human body and are distributed in blood stream to reach their actual target site. The assessment of toxicant absorption can assist in evaluating the adverse effects of any toxin or xenobiotics on different body organs. Generally, toxicants absorb through passive diffusion in which they move against the concentration gradient from higher concentrations to lower concentrations (Alagga et al., 2024). However, there are different routes of exposure as discussed below and shown in Fig 1.

Inhalation: Inhalation is considered as the primary route of absorption for various toxins including atmospheric gases and environmental pollutants. Lungs along with respiratory epithelium provides sufficient surface area for the rapid absorption of inhaled toxins (Scott, 2001). However, the rate of absorption depends upon the size, diameter, and duration of exposure of toxicant (Nahar et al., 2013).

Oral intake: Ingestion of toxicant is defined as “swallowing of toxic material which later on absorbs through the gastrointestinal tract and becomes part of the bloodstream. The small intestine provides a large surface area as well as conserved morphology for absorption. Unlike the respiratory system, the absorption in digestive track primarily depends upon the chemical configuration of toxicant and its solubility against the walls of small intestine (Wu et al., 2022).

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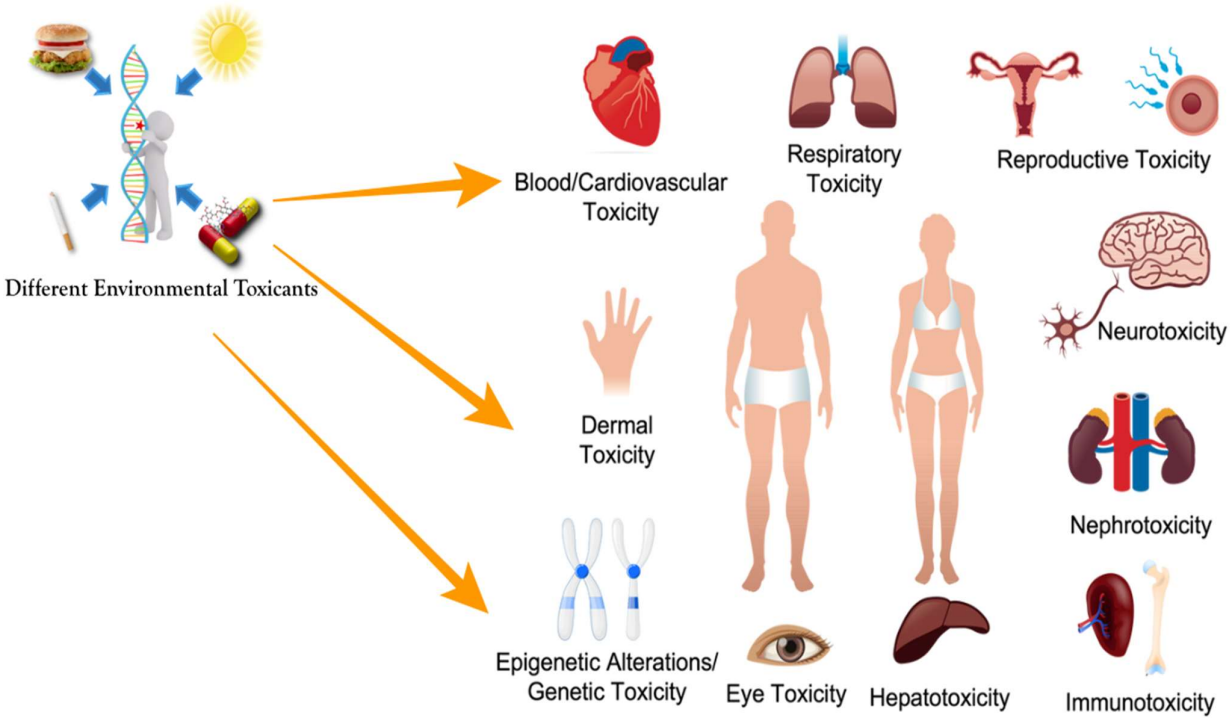

Fig 1. Penetration of toxicants and their impacts on living systems

Dermal and parenteral intake: Skin acts as a first line of defense against various pathogens and toxicants. However, micro and nano toxicants breach this defense and enter the bloodstream. The intensity of dermal absorption depends upon the type of toxicant, exposure duration as well as exposure concentration. Different factors such as injured skin (wound) escalate the rate of absorption through skin. The intentional administration of toxicants into bloodstream through injection is called parenteral absorption. Parenteral intake includes the administration through intramuscular, subcutaneous or intravenous (Tubic-Grozdanis & Krämer, 2023).

VARIOUS TOXICANTS AND THEIR MODE OF ACTION

Our body is continuously exposed to various environmental toxicants which adversely affect the normal processes. The following toxicants are well known for their toxicities.

Heavy metals

Technological advancements improved the standard of life but raised various environmental as well as health concerns in terms of safety, improper disposal, unrestrained industrialization, and pollution (Bennett et al., 2003). Heavy metals are widely used in daily life to sustain the living standard. Furthermore, natural sources are continuously releasing immense number of metals in our environment via different anthropogenic operations (Jaishankar et al., 2014; Nagajyoti et al., 2010). Since decades, heavy metal toxicity becomes a global health concern particularly in Asia (Meharg, 2004; Cheng, 2003). Metals can easily escape from various control mechanisms such as transport, homeostasis, and compartmentalization, therefore adversely affecting the body organs. These heavy metals generate excessive reactive oxygen species (ROS) which directly attacks the biomolecules such as DNA, protein, and lipids (Flora et al., 2008). There are various heavy metals which adversely affect the living system as given below:

Mercury: Mercury (Hg) is considered as the most toxic heavy metal which is released in response to different anthropogenic activities such as mining, municipal wastewater discharge, agricultural practices, discharge of industrial waste and incineration (Chen et al., 2012; Jan et al., 2009). Furthermore, it is widely used in different measuring instruments such as thermometers and pyrometers as well as in batteries. The half-life of inhaled Hg is approximately 60 days inside the body (Chang, 1977). Hg instigates various damages such as elevated heart rate, skin rashes, diarrhea, vomiting, lungs toxicities, neurological abnormalities, anxiety, tremors, nephrotoxicity, reduced muscle coordination and hypertension (Asano et al, 2000; Bates, 2003). Owing to its lipophilic nature, Hg can easily cross the bio-membranes and induces aforementioned disruptions. Though all forms of Hg are highly toxic to living tissues, their ultimate consequences depend upon their distribution and metabolism inside the body (Zalups & Lash, 1994). It is documented that humans intake Hg through different pathways such as inhalation (80%), gastrointestinal tract (< 1%) and dermal contact (3%). As already reported, Hg directly attacks lungs owing to large surface area of alveoli, but they also cross the walls of alveoli and enter the bloodstream. Moreover, the inorganic form of Hg non-uniformly distributed in the body and majority of this form accumulates in kidneys which ultimately impairs the renal functions. Various investigations evaluated the toxic effects of Hg on kidneys through estimating different parameters such as

glomerular filtration rate, presences of various proteins such as transferrin, albumin, α1-microglobullin, β2-microglobulin and retinol binding proteins in urine (Langworth et al., 1992; Cardenas et al., 1993; Franko et al., 2005; Al-Saleh & Al-Sedairi, 2012). The assessment of creatinine and blood urea levels are also used as basic parameters to evaluate Hg induced renal toxicity (Li et al., 2013). Tabular microdissection investigations have documented that inorganic Hg accumulates mainly in straight and convoluted section of proximal tubule (Zalups & Barfuss, 1990; Zalups, 1991). Moreover, inorganic Hg induces oxidative stress in nephrocytes and disrupts the normal physiology of renal tissues (Han et al., 2022).

Arsenic: Arsenic is another toxic heavy metal which adversely affects the health of humans as well as their ecosystem (Rahman et al., 2009). Acute intoxication of arsenic is associated with abdominal pain, nausea, vomiting and diarrhea (Ratnaike, 2003). It is reported that arsenic undergoes various metabolic conversion in the body therefore its mechanisms of action vary with respect to its chemical form (Molin et al., 2015; Naranmandura et al., 2011). Monomethylarsonous acid and dimethylarsonous acid are the most toxic metabolites of arsenic (Bozac et al., 2018). As intoxication disrupts the normal functions of peripheral as well central nervous system (Chen et al., 2016). Different investigations have elucidated that oxidative stress is the major culprit underlying toxicity of arsenic (Liu et al., 2013). As exposure inhibits the complex IV, II and I of electron transport chain which escalates the production of ROS (Kharroubi et al., 2017). Crossing the blood-brain barriers result in gliosis and neuronal degeneration (Selim et al., 2012). The toxic potential of arsenic is strongly associated with its high affinity for SH functional groups. Recent studies have revealed that arsenic inhibits the function of sulfur containing pyruvate dehydrogenase enzyme complex which is considered pivotal for the transformation of pyruvate to acetyl-CoA. Furthermore, arsenic binds with phosphate and blocks the mitochondrial respiration as well as synthesis of ATP. These metabolic impairments may lead to death owing to multiple organ failures (Shila et al., 2005).

Lead: Lead (Pb) is a ubiquitous environmental pollutant which poses serious threat to the health of living beings. Owing to its ductility, high malleability, and low melting point, it is extensively used in several aspects of daily life (Jacobs et al., 2009). Gastrointestinal and respiratory tracts and skin are the primary routes of Pb exposure (Levin & Goldberg, 2000). After inhalation, approximately 35-40% of Pb particles accumulate in lungs out of which 37% are deposited in alveolar region. Furthermore, 50% of inhaled particles are deposited in the respiratory track which becomes part of blood circulation (Jones, 1989). Chronic intoxication of Pb induces the iono-regulatory alterations in K+, Ca2+, and Na+ homeostasis. Owing to the high deposition rate of Pb, the Kidney and liver are most susceptible to Pb toxicity (Patra et al., 2001). Both organs are exposed to high concentrations of Pb due to their involvement in detoxification and elimination of toxic substances (Vinodhini & Narayanan, 2008; Javed, 2012; Zhai et al., 2017).

TOXICODYNAMIC

Significance of understanding how toxins interact with the body

Humans are exposed to a wide variety of compounds, both naturally occurring and man-made, that can be found in our diet, surroundings, and places of employment (Huhn et al., 2021). It is critical to comprehend how various drugs behave and interact with one another when they are present in the human body simultaneously and whether these interactions have hazardous effects. When these elements interact, they could have synergistic effects that are either greater than or equal to the toxicity of the distinct elements (Delfosse et al., 2021; Elcombe et al., 2022). Following are some well-known toxicants that interact with biological systems in diverse ways:

Paraquat

After absorption, paraquat reaches into peak plasma concentration and distributes rapidly to highly vascularized tissues like Clara cells, lung tissue, specifically targeting type 1 and 2 pneumocytes in the bronchial tubes as well as highly permeated tissues like the liver, skeletal muscles, urinary tract, and heart. Moreover, there is still a little remaining PQ in the ventricular area which is defined by a distribution volume that is fallen between 1.2 and 1.6 L/kg. Paraquat accumulates in the respiratory tract significantly in the polyamine transport system (PTS). Research using histopathological and autoradiographic methods, however, have found that PQ mostly found in pulmonary tissues and bronchioles which are noticeably missing from macrophages (Wang et al., 2021; Gawarammana et al., 2011). With a half-life range between four to six hours, PQ demonstrates its binding affinity to serum proteins and spread quickly to different tissues of the body. However, it is particularly abundant in cells of the alveolar membrane. On the other hand, peak concentration in the blood usually appears six hours after its consumption. After that, renal clearance significantly reduces, especially in situations of acute intoxication. As a result, over the period of days to months, the renal system gradually eliminates a portion of PQ that has gotten into more deeply embedded tissues (Oliveira et al., 2008; Sahu et al., 2020).

The main process by which the PQ aggregates in airway tissues is active transport especially polyamine transport (PT), which is used for moving polyamines such as putrescine, superamine and superamine. Noticeably, PQ is around five times more concentrated in lung tissues than in plasma. However, the alveolar region, epithelial cells and polyamine consumption pathways help in PQ absorption in the lungs. The structural resemblance between PQ and endogenous diamines accounts for this absorption (Rashidipour et al., 2020). Nevertheless, studies show that PQ preferentially aggregates in airway tissues, causing substantial fibrosis. Furthermore, the lungs have a significantly longer initial half-life of PQ than other organs (Hwang et al., 2002). After administration, PQ displays diverse placement patterns in different organs. It primarily determines the medulla within the thymus between two hours and seven days after its administration. On the other hand, PQ primarily places in the red pulp of the spleen for about 10 days after administration. Furthermore, PQ migrates

to mucosal lamina propria and epithelial cells in the esophageal cell. Finally, within three hours after its ingestion, epithelial cell localization becomes apparent in the colon. After ingestion, PQ becomes concentrated in the kidney distal tube and hepatocytes (Rashidipour et al., 2020).

Paraquat has the potential to build up inside kidney tubular cells and eventually causes damage to proximal tubules of the cell. However, kidneys are essential for the excretion of PQ outside from renal system, so that any damage to them can hinder this process and increase the toxicity of PQ to other organs. Nonetheless, kidney cells actively contribute to the excretion of PQ from the bloodstream through urine. Moreover, elevated blood PQ levels, however, have the potential to cause tissue damage (Weng et al., 2017; Shabrina et al., 2023). Paraquat is abrasive which causes approximately all gastrointestinal injuries in those who are impacted by it. Moreover, by stimulating salivary gland secretion, caustic esophageal injury could increase serum amylase level. However, higher PQ levels cause gastrointestinal distress, which in turn causes elevated levels of bilirubin and hepatic enzymes (Zhang et al., 2012).

Perfluoroalkyl substances (PFAS)

Perfluoroalkyl substances (PFAS) are synthetic compounds which have been used worldwide since the 1940s (Paul et al., 2009). They are very stable when exposed to heat and chemicals and work well as surfactants. These properties make them useful in many commercial processes and goods (Buck et al., 2011). Although 3M is the largest manufacturer of perfluorinated chemicals, and has stopped producing PFOS, this pollutant is still found globally in wildlife and humans because it persists in surroundings and accumulates in living things (Hansen et al., 2002). The primary negative impact of PFOS is liver damage, nerve damage, reproductive damage, immune system damage, thyroid problems and heart toxicity. The most important and largest organ of the human body is the liver which plays a key role in detoxification (Han et al., 2018). PFOS can cause liver damage, leading to fatty liver, an enlarged liver, increased liver cell growth and oxidative damage in liver cells (Du et al., 2009).

Neurotoxicity occurs when neurotoxins, which are harmful substances (natural or synthetic), cause damage to the composition and functionality of neurological system (Rock & Patisaul, 2018). Studies in living organisms have shown that PFOS administration can lead to problems with motor skills, learning, memory and thinking abilities (Chen et al., 2014). Harmful effects on a living organism's reproductive system are referred to as reproductive toxicity (Ayoka et al., 2016). Exposure to PFOS can damage male and female reproductive organs, disrupt hormone levels, and have a negative impact on the success of conceptions (Yang et al., 2016).

Immunotoxicity refers to harmful effects on immunity, which includes immune organs, immune cells, and immuno-active substances. This can result in immunosuppression, overstimulation, allergies, or autoimmune diseases (Shao et al., 2014). PFOS can disrupt the growth, development and proper function as well as interfere with the production and action of chemicals that are immune-active (Soloff et al., 2017). Damage to the heart and blood arteries is referred to as cardiac toxicity. Exposure to PFOS can lead to heart defects, alter heart rate, and cause heart muscle cell death (Liang et al., 2017). The cardiovascular system is particularly sensitive to chemicals during its development, so many studies examine PFOS's effects on embryos or prenatal exposure.

CONCLUSION

Toxicokinetic and toxicodynamic laid the foundation of toxicological sciences. These fundamental concepts explain how a toxicant or drug enter the living system and how these substances interact with our body. These concepts are essential during risk assessment of any drug or environmental toxicant to evaluate the action of that particular substance. These studies elucidated that toxicity of any substance depends upon its mode of penetration, duration as well as mechanism of action. Therefore, understanding the core concept of toxicokinetic and toxicodynamic covers the entire concept of toxicology.

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