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A REVIEW ON MECHANISMS IN DRUG-INDUCED HEPATOTOXICITY

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ABSTRACT

The withdrawal of a number of commonly prescribed medications from the market on the grounds of hepatotoxicity has garnered significant attention. Techniques to more accurately assess hepatic risk before receiving federal approval are currently undergoing a thorough evaluation. Prescribers and patients need to exercise a great deal of caution and education when evaluating the risk-benefit ratios associated with innovative agents that have hepatotoxicity concerns, particularly when those agents are used to treat life-threatening conditions. Drug-induced liver injury can mimic nearly all liver illnesses that are currently unknown. When it comes to the type of injury (hepatocellular versus cholestatic) and the timing of onset, drug-induced liver injuries frequently exhibit a rather distinctive signature. When diagnosing drug-induced liver damage, suspicion is sometimes founded on circumstantial evidence and is first based on exclusion.. Drug-induced liver damage can occur through a wide range of mechanisms. The intermediate metabolites that are created during the metabolism of many medications are extremely hazardous and reactive. Hepatic damage may or may not occur in these circumstances depending on how the drug's effectiveness and the metabolite's rate of generation interact.

Key words: medicines, liver damage, and hepatotoxicity.

1. INTRODUCTION

The liver performs a staggering number of essential roles in the upkeep, operation, and control of the body's homeostasis. Nearly every metabolic route leading to development, illness prevention, nutrition supply, energy production, and reproduction is impacted by it [1]. The metabolism of carbohydrates, proteins, and fats as well as detoxification, bile secretion, and vitamin storage are the liver's primary roles. For this reason, maintaining a functioning liver is essential to general health and wellbeing [2]. A major contributing factor to liver damage is drug use. There have been reports of over 900 medicines, poisons, and plants causing liver damage; of these, pharmaceuticals are responsible for 20–40% of cases of fulminant hepatic failure.

Roughly 75% of the unique medication reactions end in liver transplantation or even death. The incidence of DILI is likely higher than the reported range of one in 10,000 to one in 100,000 patients due to underreporting and missed diagnoses [3].

Hepatotoxicity is the term for liver damage caused by chemicals. Some medications have the potential to harm an organ when taken in excess or occasionally even when administered within recommended dosage ranges. Hepatotoxicity can also be caused by other chemical agents, such as those employed in factories and labs, natural compounds (such microcystins), and herbal medicines. We refer to substances that harm the liver as hepatotoxins. More than 900 medications have been linked to liver damage, which is the most frequent cause of a medication's removal from distribution.[4].

2. DEFINITION

A disorder called hepatotoxicity, sometimes referred to as liver toxicity, is characterised by liver damage brought on by exposure to hazardous substances, chemicals, or certain drugs. Damage to the liver may result in decreased liver function and, in extreme situations, liver failure.

Types of Hepatotoxicity

Hepatotoxicity comes in two flavours: the less common intrinsic reaction, which is dose-dependent and predictable, and the more common idiosyncratic reaction, which is neither dose-dependent nor predictable.

1. Intrinsic Hepatotoxicity: This term describes liver damage that is directly brought on by a substance's natural characteristics. This kind of dose-dependent hepatotoxicity typically happens when the offending chemical is exposed for an extended period of time or at large concentrations.

- Direct Cellular Injury: Hepatocytes are susceptible to direct chemical damage, which can result in cell death and malfunction. For instance, the creation of hazardous metabolites during an acetaminophen overdose results in hepatocellular necrosis.
- Mitochondrial Dysfunction: In liver cells, certain medications and poisons destabilise the mitochondria, reducing their capacity to produce energy and initiating the processes that lead to cell death.

Oxidative Stress: When chemicals or medications produce too many reactive oxygen species (ROS), the liver's antioxidant defenses are weakened, leading to oxidative damage to cellular constituents [29,30]

2. Idiosyncratic Hepatotoxicity: This condition is typified by erratic liver damage that affects a tiny percentage of people who are exposed to a certain chemical. Idiosyncratic responses can happen at therapeutic dosages and are not dose-dependent like intrinsic hepatotoxicity. Idiosyncratic hepatotoxicity is caused by the following mechanisms:

- Immune-mediated Reactions: When certain medications or their metabolites are identified by the immune system as foreign antigens, liver cells may become the target of an immunological-mediated assault. T-cell activation, antibody generation, and pro-inflammatory cytokines are all involved in this process. Genetic Susceptibility: Individuals are predisposed to idiosyncratic reactions due to a variety of genetic causes. Human leukocyte antigens (HLAs), immune response genes, and drug-metabolizing enzyme polymorphisms can all affect a person's vulnerability to idiosyncratic hepatotoxicity [30-31]

Pathophysiology

Because of its important function in drug metabolism, the liver is frequently involved in drug toxicity [5]. DILI is a multi-step process that includes activation of inflammatory pathways after direct drug damage. This event in a specific environmental context, along with a person's genetic predisposition, creates the conditions necessary for the development of cellular and host harm [6].The offending drug, or more frequently, drug metabolites, initiates the earliest stages of damage. The polymorphic cytochrome P450 (CYP450) family of proteins and phase I drug metabolism frequently produce the hepatotoxic metabolites. On the other hand, conjugative phase II metabolism could potentially produce the hazardous chemicals.

The drug's following effects on cells, mitochondrial inhibition, and/or certain immunological responses then serve to spread the damage. Numerous processes, such as glutathione depletion or the binding of metabolites to lipids, nucleic acids, enzymes, or other structures, can cause direct cell stress. Reactive oxygen species (ROS) build up and ATP is depleted as a result of direct mitochondrial inhibition, which is the uncoupling or inhibition of the mitochondrial respiratory chain[7]. The medication or its metabolite can elicit specific immunological responses by attaching to HLA proteins, which T cells then encounter and identify as antigens. After then, the neo-antigens are deposited on antigen-presenting cells to trigger the immune system to produce autoantibodies against cell structures or to initiate the production of antibodies against oneself.[8]

It is stated that reactions only happen when a second signal—often referred to as the "danger signal"—occurs[9].It is believed that this signal triggers signaling pathways that lead to immune-mediated liver injury through oxidative stress or cell destruction. A different medication, a host factor like a bacterial or viral infection, or the release of cytokines during an inflammatory response could all be the signal.According to research, a minor inflammatory response is frequently the "danger signal" that leads to liver damage[10 ,11]. Low dose lipopolysaccharide increased the hepatotoxic potential of recognized hepatotoxic substances.

Mitochondrial permeability transition (MPT) is the final result of all these processes, including immunological activation, mitochondrial inhibition, and cell stress. By increasing permeability and proton influx across the inner membrane, MPT damages mitochondrial membranes and impairs the generation of ATP. Together with the release of cytochrome C and other pro-apoptotic proteins into the cell cytoplasm, this disruption also results in an expansion of the mitochondrial matrix and an increase in the permeability of the outer mitochondrial membrane [12]. There are two ways in which immune responses and cell stress achieve this. The direct mechanism that activates pro-apoptotic proteins and inhibits anti-apoptotic proteins to activate MPT is started by cell stress. Immune responses trigger the extrinsic route, which results in the production of TNFα and FAS ligand (FasL) by Kupffer cells upon antigen presentation. The death-inducing signaling complex (DISC) is formed when TNFα and FasL connect to intracellular death receptors and death domain proteins, activating caspase 8. Additionally, Caspase 8 stimulates the pro-apoptotic Bcl-2 proteins, which together with the DISC complex cause MPT[13]. Cellular necrosis or apoptosis is the last stage of injury. Apoptosis is an ATP-dependent process that can only take place in the event that MPT does not happen quickly and uniformly in every mitochondria in the cell. Apoptosomes are formed when cytochrome c binds pro-caspase 9 and a cytoplasmic scaffold protein in the presence of ATP. This process activates caspases, leading to nuclear and cytoplasmic condensation and fragmentation. Phagocytosis is then used to eliminate the pieces. Apoptosis proceeds without loss of plasma membrane integrity, significantly reducing inflammation and resulting in little collateral damage [12]. MPT's significant disruption of mitochondrial activity and ATP depletion lead to necrosis. After significant disruption of cell processes, bleb development, actin oxidation, microfilament breaking, cellular swelling, and ultimately rupture of the plasma membrane occur [13].

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GENERAL MECHANISMS OF HEPATOTOXICITY

DILI is typically divided into two categories: idiosyncratic hepatotoxicity (IDHLI) and allergic vs. non-allergic hepatotoxicity (IDLI). Idiosyncratic hepatotoxicity happens in an unpredictable way and lacks apparent dosage dependence, whereas intrinsic hepatotoxicity is thought to be dose dependent and predictable over a rough threshold dose. The symptoms and indicators of adaptive immune reactions, such as fever, skin reactions, eosinophilia, autoantibody production, and a brief latency period, especially following re-exposure, are indicative of allergic idiosyncratic hepatotoxicity. Acute vs chronic onset, severity, histological criteria, hepatocellular, cholestatic, or mixed liver enzyme patterns are among the other clinical classifications that distinguish. These classifications are helpful in clinical practice because they outline the typical clinical signs of DILI for particular medications and can provide helpful cues about the relevant mechanisms.

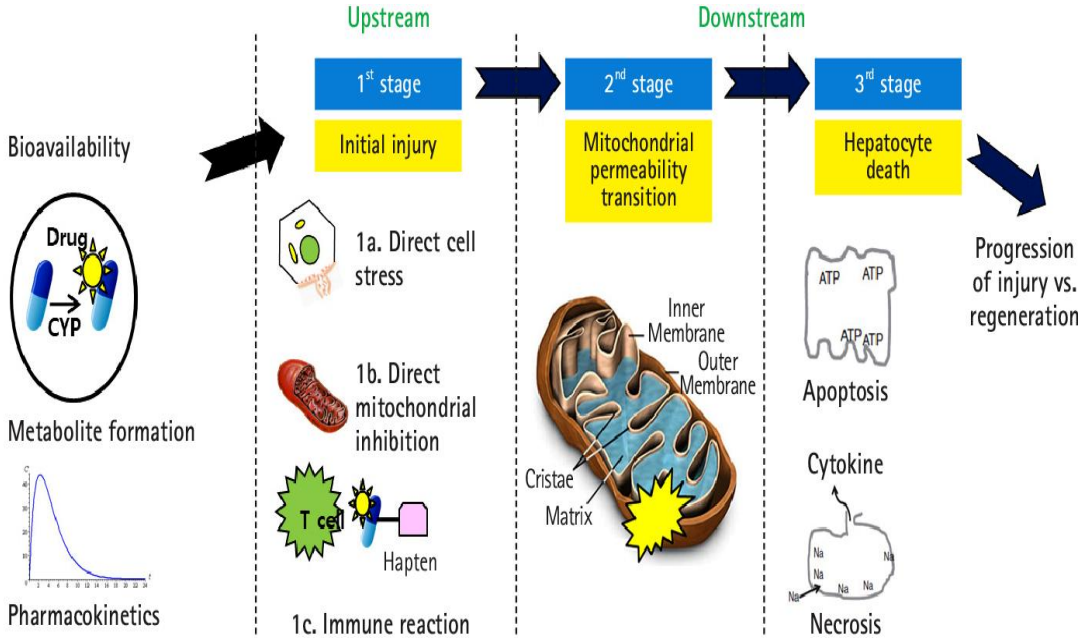

Fig.1 Mechanism of drug-induced liver injury. The hepatocyte injury mechanism is divided into three stages: [32]

1. Initial Mechanisms of Toxicity: Direct Cell Stress, Direct Mitochondrial Impairment, and Specific Immune Reactions

Firstly, drug metabolites, or less frequently, parent medicines as well, can directly stress cells, interfere with mitochondrial function, or set off particular immunological responses. The polymorphic cytochrome P450 (CYP450) family, which mediates oxidative phase-I drug metabolism, is the most significant drug-metabolizing enzyme system for the production of hepatotoxic reactive metabolites. But conjugative phase-II metabolism can also produce metabolites that are harmful to the liver; for example, acyl glucuronides are widely recognized to induce DILI [14,15].

Reactive metabolites have the ability to cause early cell stress in a variety of ways, such as via binding to enzymes, lipids, nucleic acids, and other cell components or by depleting glutathione (GSH). Additionally, parent medications or reactive metabolites may selectively impede other hepatocellular processes including the apical (canalicular) bile salt efflux pump (BSEP, ABCB11 gene), which could lead to secondary toxic hepatocyte damage from the intracellular buildup of its substrates [16].

2. Direct and Death Receptor-Mediated Pathways Leading to Mitochondrial Permeability Transition

Second, MPT is caused by first immunological responses and/or initial cell stress. There are two main ways in which the initial mechanism can affect mitochondrial function without directly targeting it: either through an intrinsic pathway, which is triggered by severe cell stress, or through an extrinsic pathway, which is triggered by mild cell stress and/or certain immune reactions. Severe intracellular stress triggers the endoplasmic reticulum route, lysosomal permeabilization, or c-jun N-terminal kinase (JNK) in the intrinsic pathway [17-21].

3. Apoptosis and Necrosis

Third, damaged mitochondria cause apoptosis or necrosis in cells by reducing their ability to produce energy. Mitochondrial ATP synthesis is halted when a large amount of protons are allowed to pass through the inner mitochondrial membrane due to MPT. Matrix expansion, mitochondrial outer membrane permeabilization, and rupture due to mitochondrial ATP depletion brought on by MPT (or other direct mechanisms of mitochondrial damage previously mentioned) release cytochrome c and other pro-apoptotic mitochondrial proteins into the cytosol from the intermembrane space [17,22-25]

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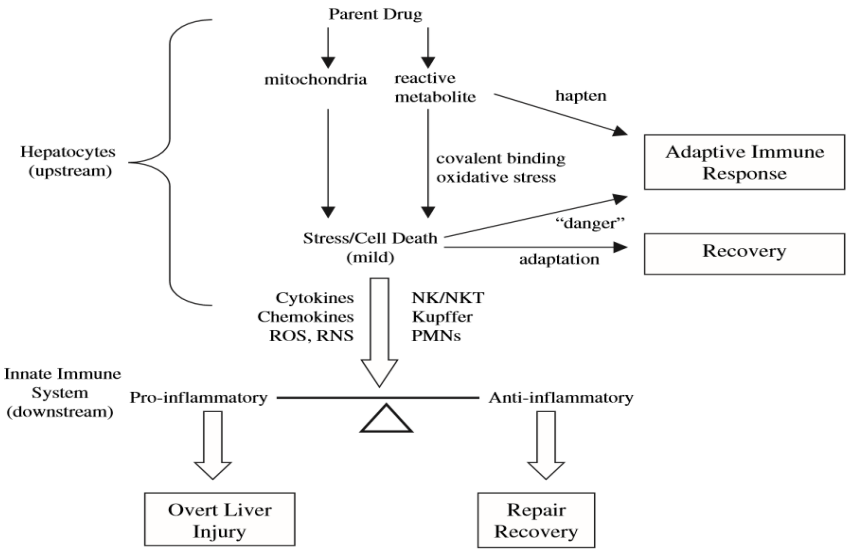

Protective Mechanisms and Regeneration

Intrinsic and extrinsic mechanisms, as well as the ensuing development of necrosis and apoptosis, are modulated by other variables and pathways. TNF, on the other hand, also triggers nuclear transcription factor kappa B (NF-B)-dependent survival gene production in addition to its DISC-mediated harmful effects[25]. JNK is inhibited and antioxidant gene overexpression is encouraged by NF-B responsive genes. Similarly, nuclear factor erythroid-derived 2-like (NFE2L, commonly known as Nrf2) upregulates antioxidant genes that guard against cell damage in response to oxidative stress.[26] Glutathione (GSH), in particular, is an antioxidant that is essential for cell defense against DILI. GSH is a crucial scavenger of reactive metabolites, such as N-acetyl-p-benzoquinone imine (NAPQI), a poisonous metabolite of APAP produced by CYP450 2E1, as well as ROS from a variety of sources in the mitochondria and cytoplasm. Thus, the main defense mechanism for treating APAP-intoxication with the GSH precursor N-acetylcysteine is replenishment of GSH stores. Moreover, GSH seems to influence other harmful or protective pathways indirectly, such as the need for high GSH levels for the production of the NF-B-activated survival gene [27,28].

3. CONCLUSION

In conclusion, a number of pathways both start and exacerbate processes that already cause injury to liver cells. A common target for the hepatotoxicity of several medications is the mitochondria. When these essential cell organelles malfunction, energy metabolism is hampered and an intracellular oxidant stress with increased reactive oxygen species and peroxynitrite production occurs. Apart from mitochondria, oxidative stress and cell damage are also encouraged by the stimulation of cytochrome P450 isoenzymes, like CYP2E1. Bile acid buildup results in further stress and cytotoxicity if hepatocellular function has been compromised. Neutrophils are drawn into the liver by Kupffer cells, which are also activated by cell damage, gut-derived endotoxins, or a mixture of the two. Even though they are in charge of clearing away cell debris and are a component of the host defense system, these inflammatory cells can occasionally cause further liver damage.

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