

Development on Animal Models for Drug/Chemical Induced Liver Injury

Deepika Bhatia¹, Yogeeta¹, Pradeep Goyal² and Atul Kabra^{1*}

¹University Institute of Pharma Sciences, Chandigarh University, Mohali, Punjab, 140413, India.

²Saraswati institute of pharmacy, Mohali, Punjab, 140413, India.

*Corresponding Author E-mail: Bhatia.deepika89@gmail.com

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In the human body, the largest gland is the liver and does a lot of essential work of the body. Liver damage is the cause of mortality and increasing day by day. Liver disease is caused by multiple factors, such as an autoimmune condition, toxic chemical exposure, viral infection, and dietary factors. Drug-induced liver injury (DILI) is a critical issue in drug development because DILI causes failures in clinical trials and the withdrawal of approved drugs from the market and leading to pathological changes result, including increase in SGOT, SGPT and bilirubin as well as the free radical generation. In this review, contains the animal model of hepatotoxicity with a different cause, their action mech., and procedure with dose. These models include the toxicity caused by chemical, drug, radiation, metal, diet, and high-fat this will lead to pathological changes resulting in hepatotoxicity.

Keywords: Animal Models; Hepatotoxicity; Liver; Liver Damage.

In the human body, the largest gland is the liver and has an important role in our body. From metabolism to the production of minerals, vitamins storage, homeostasis, proteins, storing glucose and fat from the diet, remove RBC (red blood cell) which are damaged or dead through the spleen. The main work of the liver is to remove the toxins present in the human body while doing the metabolism of toxins; toxins accumulate in life as the accumulation rate is higher than the rate of metabolism. And that cause damage to the liver¹. The damage of liver causes alteration in the functioning of the liver and causes pathological changes in it. Death of liver cell, increase in the oxidative stress, liver got fatty, accumulation of triglyceride in the form of vacuoles, impairment

in bile production, inflammation in the liver, obstruction of small hepatic nerves, increase in the level of CRP (c-reactive protein), ESR (*erythrocyte sedimentation rate*), PV (Plasma viscosity), cancer of liver further these changes in the liver causes increased pressure into portal vein and liver failure.²

Etiology

There are many reasons for liver damage. It can be induced by the drug, by chemical, also by herbal or dietary supplements.

Drugs that cause toxicity: Non-steroidal anti-inflammatory Drugs *i.e.* Paracetamol, anti-cancer drugs, anti-Tuberculosis, antibiotics.

Chemical that causes toxicity: CCl₄ (Carbon tetrachloride, thioacetamide), DEN (diethylnitrosamine), aflatoxin B₁.

Metals that cause toxicity: cadmium, mercury, arsenic.

Toxicity induced by radiations, alcohol, diet, high-fat diet.

Risk factors

Gender, age, concomitant medications, alcohol, nutrition, hepatitis B and C, and genetic factors.^{3,4}

Experimental Models For Hepatotoxicity

Animal models are used as they have similarities with the function of the human body and play a major role in the experimentation. These models include the toxicity caused by chemical, drug, radiation, metal, diet, and high-fat food-induced.

Toxicity caused by chemicals

Some chemicals like CCl_4 , TTA, DEN cause hepatotoxicity. These metabolites lead to some changes in the biological function and physiology of the liver. GSH and neutrophils are found to have a major role in the induction of liver damage by chemicals.

CCl_4

Carbon tetrachloride (CCl_4) caused toxicity. It is an inorganic compound.

Mech. of action

It is a well-known toxicant for liver toxicity. CCl_4 after metabolism converts to CCl_3 and it is produced by CYP2E1 in the liver cell. This is a free radical that binds with the cellular proteins and lipids, and trichloromethylperoxyl radical forms. This causes necrosis of centrilobular tissue present in the hepatic lobule³. It is studied in the histopathology that after 2-4 weeks fibrosis occurs significantly and after 5-7 weeks serious

bridging fibrosis, and after 8-9 weeks onset of cirrhosis occurs.

Procedure

Rats of any gender are given a regular diet and water at the temperature of $25 \pm 2^\circ\text{C}$. Animals are left empty stomach, before the experimentation. For causing hepatotoxicity, CCl_4 with different doses through a different route and in different periods was administered. On the end day of experimentation animals were sedated, the sample of blood was collected, liver enzyme activity was carried out, and they were killed after that histopathological and biochemical parameters were studied^{5,9}.

TAA

TAA is an organophosphorus solid, white crystalline compound, which is soluble in water and is a source for sulfide ions in the production of inorganic and organic compounds¹². It can also be used for causing fibrosis and also it causes injury to zone 3 and 1 hepatocytes¹³.

Mechanism Of action

It is not harmful to the liver, but thioacetamide-s-oxide, a TAA intermediate metabolite, covalently binds to hepatic macromolecules, altering cell permeability and increasing intracellular Ca^{2+} concentrations, causing cellular damage and necrosis in both zone 1 and zone 3 hepatocytes. At low doses, TTA induces the formation of cirrhosis and portal central septa or portal-portal septa. When it is compared with the other hepatotoxins, TAA therapy took much time to generate substantial fibrosis, whereas other hepatotoxins increase the chance of test animals dying prematurely by the progression of cholangiocarcinoma and HCC (hepatocellular carcinoma)^{13,14}.



Fig. 1. Healthy liver and liver with cirrhosis

Procedure

Animal of any gender were given the proper diet and given adequate water before the experiment, and they were kept in an environment where the temperature is being controlled with a 12-hour of the dark and light cycle. The rats were given TAA in various concentrations, methods, and periods to induce TAA-induced hepatotoxicity. The animals were sedated on the final day; the sample of blood was obtained, centrifuged. After that, the liver serum enzyme activities were performed.

DEN (diethyl nitrosamine)

The majority of nitrosamines, which have the chemical structure $R_1-N(-R_2)-N=O$, are cancer-inducing agents. It's utilized for the production of insecticides, in the majority of rubber products, and cosmetic products. It can cause cancer in a wide range of animal species, implying that it may also cause cancer in humans¹⁹.

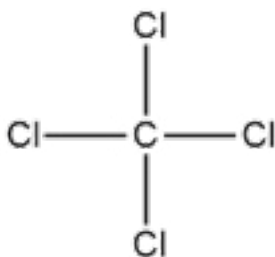
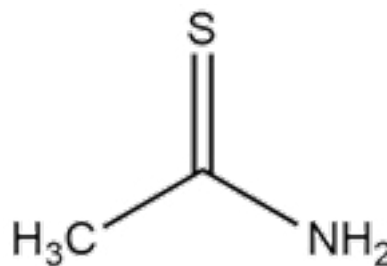
Mechanism of action

DEN is frequently used for inducing cancer. Diethyl nitrosamine is hydroxylated by

CYP2E1 in the liver to produce ethyl diazonium ion, a bioactive intermediate that causes alteration in DNA by interacting with the nucleophiles, resulting in hepatocyte necrosis around the vein and periportal areas, as well as Centro-portal fibrotic septa. HCC is caused by low doses of DEN given for a long time period^{20,21}. As a result, this model is particularly useful for research on the development of liver HCC from fibrosis.

Procedure

Animal of any gender was maintained in cages and given free access to food and tap water in a controlled environment (25° C and with the 12 h dark and light cycle). Animals will be administered by varying doses of DEN to develop hepatotoxicity (50mg –200 mg per kg, by route *i.p.* for a period of 4–12 weeks) to create hepatotoxicity^{22–24}. The animals were sedated on the last day, blood samples were obtained, and centrifuged, and serum samples were separated for the assessment of hepatotoxicity indices. After that, animals were euthanized, and

**Fig. 2.** Structure of carbon tetrachloride**Fig. 3.** Structure of Thioacetamide**Table 1.** Hepatotoxicity caused by CCl_4

Animal used	Dose	Route	References
Male Sprague-Dawley rats	0.5 ml/kg for 3 days	<i>i.p.</i>	[6]
SpragueDawley rats (male)	0.2 ml per 100gm for 2 weeks	<i>i.p.</i>	[7]
Wistar (male) rats	0.5 ml per kg two time in 7 days (for 4 weeks)	<i>i.p.</i>	[8]
Wistar (male) rats	0.125ml per kg for 7 days	<i>i.p.</i>	[9]
Albino rats of Wistar strain	1.0 ml per kg after every 3 rd day for a period of 10 days	<i>i.p.</i>	[10]
Wistar (male) rats	2 ml per kg, on every 3 rd day for a period of 10 days	<i>s.c.</i>	[11]

Table 2. Hepatotoxicity caused by TTA

Animal	Dose	Route	References
Wistar rat (male)	TTA 200 mg per kg, for the time period of 12 weeks	<i>i.p.</i>	[15,16]
Wistar rat (male)	Thioacetamide 300 mg per kg, on 14 th day	<i>i.p.</i>	[17]
Wistar rat (male)	Thioacetamide 400 mg per kg, for 2 weeks	<i>i.p.</i>	[18]

the livers of animals were extracted for studying various morphological and molecular analyses.

Hepatotoxicity caused by drug

Toxicity caused to the liver by the drug can be severe, life-threatening, and can create a severe condition to hospitalization. These reactions can be predicted or unpredicted. Predictable reactions are the reaction noted before or have the possibility to occur inpatient due to the dose of the drug or the drug exposure. Unpredictable hepatotoxicity is the unusual response of drugs that are not noted in clinical trials, they can occur in a few days to months, not compulsory to occur by dose. There are two broad categories of hepatotoxicity- 1st is the injury caused by the drug or by its metabolites (critical cellular functions are altered by causing injury to hepatic cell. Second is the condition in which drug metabolites directly cause toxicity by sensitizing the hepatic cell to cytokines-induced injury.

Among the drug which causes hepatotoxicity NSAIDs are the most commonly causing liver injury. These drugs are mostly prescribed to the patient for pain including arthritis, acute musculoskeletal disorder, a wide range of inflammatory conditions, and trauma resulting from painful conditions²⁵. The mechanism of these drugs on which they work is anti-inflammation, antipyretic, and analgesic. These drugs mostly cause toxicity by overdose or long-

term use and show their side effects to the liver, GIT, and kidneys^{26,27}.

PCM

PCM is also known as acetaminophen. It is mainly used as an analgesic, antipyretic. But at the same time at higher doses, it causes toxicity to the body.

Mechanism of action

PCM converts to inactive compounds through Phase 2 metabolism by coupling with glucuronide and sulfate. A portion of PCM was oxidized through enzyme cytochrome P450. Then CYP2E1 & CYP3A4 convert it into NAPQI. This Semiquinone radical is formed by the reduction of one electron of NAPQI, covalently bond to cellular membrane macromolecules, and enhance lipid peroxidation, causing tissue damage. NAPQI and acetaminophen at higher doses can oxidize and alkylate the intracellular GSH (glutathione), which causes depletion of the GSH pool in the liver that leads to liver oxidation by increased lipid peroxidation^{28,29}.

Procedure

Rats of any gender are fed with regular diet and given access to unlimited water. Before use, they were given a 12-hour light/dark cycle to adapt to. PCM was given at various levels (3 mg per kg, by *p.o.* for a period of 7 days for 3 weeks) to induce hepatotoxicity³⁰⁻³⁴. Parameters for toxicity were tested. On the last day of experimentation, animals were sedated, the sample of blood was collected, liver enzyme activity was carried out.

Hepatotoxicity induced by anticancer drug

Cancer causes numerous physiological changes in the liver that further cause malignant tumors. The occurrence of neoplasia is the endpoint of cancer, biologically³⁵. Many new cytotoxic chemotherapeutic agents have been developed in recent

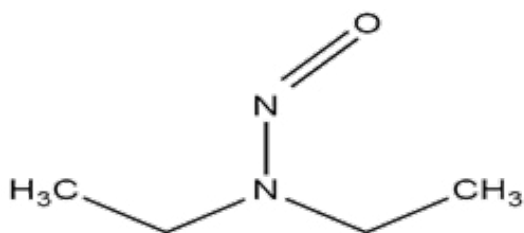


Fig. 4. Structure of DEN

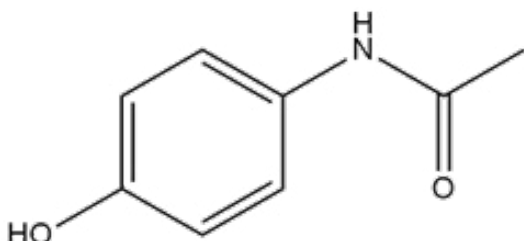


Fig. 5. Structure of Paracetamol

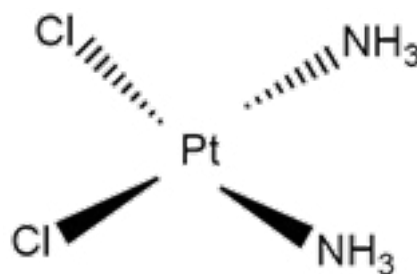


Fig. 6. Structure of Cisplatin

decades to prolong the lives of patients with advanced or metastatic tumors. Along with chemotherapy biological agents and specifically targeted antibodies are given in combination to increase the life of the patient³⁶. The anticancer drug induces tumor cell apoptosis by the production of secondary ROS and causes liver injury³⁷.

Cisplatin

It is commonly used as an anticancer agent.

Mechanism of action

Cisplatin is commonly used as an anticancer agent. Cisplatin causes toxicity by mainly two mechanisms drug metabolism or oxidative stress. Some genes and proteins help in the metabolism of the drug and cause hepatotoxicity, Like CYP 450. Proteins like CYP2D5, CYP2D1, AND CYP2C13 and genes like CYP4A1 and CYP2E1. Elevation in this enzyme and genes causes an increase in oxidative stress and ROS which causes hepatotoxicity³⁸.

Procedure

Animals were taken into the 12 hrs of the day and light cycle at the room temp (23±2°C) and access to water and food is free. Hepatotoxicity caused by given different concentration conc. of 3.5mg -7 mg per kg via *i.p.* route for one to 5 days³⁹⁻⁴². At the end of the experimentation, animals were sedated and blood samples were collected. After that liver is taken out from the animal body to estimate the antioxidant parameters and histopathological studies were done.

Methotrexate

It is earlier known as amethopterin, it is effective as an immunity suppressant and

chemotherapeutic agent. It is also used in the treatment of autoimmune disease, medical abortion, and autoimmune disorders.

Mechanism of action

It acts by inhibiting the enzymes that are thymidylatesynthetase, phosphoribosyltransferase, dihydrofolatereductase

It inhibits cell division by inhibiting nucleotide synthesis.

By causing cellular arrest it inhibits the synthesis of the DNA and RNA and by fibrosis.

Procedure

Animals were taken into the 12 hrs of the day and light cycle at the room temp (23±2°C) and access to water and food are free. Hepatotoxicity caused by given diff. conc. Of 20mg/kg/ip in single dose. At the end of the experimentation, animals were sedated and blood samples were collected. After that liver is taken out from the animal body to estimate the antioxidant parameters and histopathological studies were done⁴³.

Hepatotoxicity induced by Antibiotics

Antibiotics are microorganisms produced. Antibiotics are effective on the low concentration that selectively kill or inhibit the growth of the microorganism. They are also classified on the mech of action antibiotic which causes cell death care called bactericidal antibiotic and those which inhibit the growth of bacteria are called as a bacteriostatic antibiotic⁴⁴.

Erythromycin

It belongs to the macrolide antibiotic class. It is the most common family used against gram-positive bacteria like Streptococcus pneumonia, Staphylococcus aureus, and Hemophilus influenza⁴⁵.

Table 3. Hepatotoxicity caused by DEN

Animal	Route	Dose	References
Albino rat	<i>I.p.</i>	50-200mg per kg for 4 to 12 wk	[22-24]

Table 4. Hepatotoxicity caused by PCM

Animal	Dose	Route	References
Rat, mice	500 mg per kg	Orally on the 3 rd and 5 th day	[31]
Wistar rat	3 gm per kg	Per orally	[32]
Rat	3 mg per kg for 7 days for 3 weel	Per orally	[33]
Pregnant mice	300-400mg per kg	<i>i.p.</i>	[34]

Mechanism of action

Erythromycin A is a compound that is 14- membered ring in shape. It shows both activities bacteriostatic and bactericidal. At low concentration, it is bacteriostatic and at high conc. it is bactericidal. It interferes in protein production by binding the 50S subunit of the ribosome and translocation of susceptible cells is inhibited⁴⁶.

Procedure

Animals were taken in 12 hrs a day and light cycle at the room temp ($23\pm 2^{\circ}\text{C}$) and access or water and food are free. 100 mg per kg, *viap.o.* given for a period of 14 days to induce hepatotoxicity^{47,48}. On the end day collection of blood samples done and biomarker enzymes of the liver are estimated. After that liver of the animal is

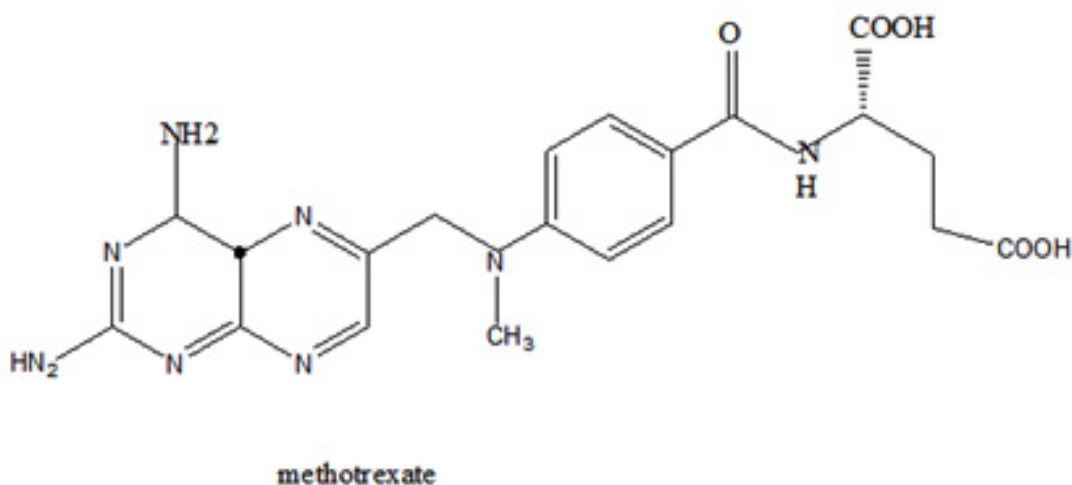


Fig. 7. Structure of Methotrexate

alcohol dehydrogenase (ADH) in the mitochondria of hepatocytes⁷¹. As soon as alcohol leaves the small intestine, it travels to the liver where it is converted into acetate by two enzymes: (a) ADH in the mitochondria of hepatocytes (b) ADH present in the cytosol.

Alcohol is converted into acetaldehyde

Table 5. Hepatotoxicity caused by Cisplatin

Animal	Dose	Route	References
Albino rat	3.5 mg per kg	<i>i.p.</i>	[39]

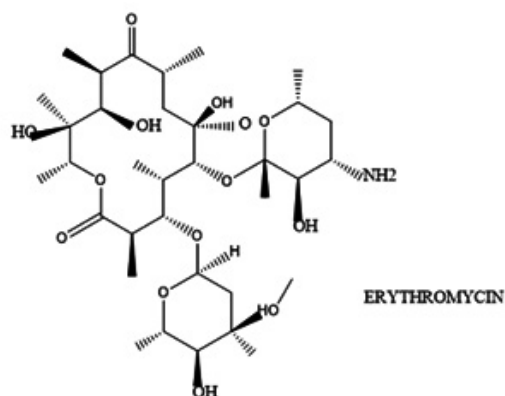


Fig. 8. Structure of Erythromycin

Table 6. Hepatotoxicity caused by Methotrexate

Animal	Route	Dose	References
Albino rat	<i>i.p.</i>	20mg/ kg/ single dose	[43]
Rabbit	<i>i.p.</i>	20 mg/kg for 3 days	[43]
Rat	<i>p.o.</i>	100ug per kg for 4 weeks	[43]

removed to estimate the antioxidant parameter and for the study of histopathological parameters.

Hepatotoxicity induced by anti TB drug

A patient suffering from tuberculosis have to take medicine for a period of 4 to 8 months, it is a long duration and these drugs may cause side effect in the body. The most common drug used for TB is isoniazid and rifampicin and these causes side effect too. Isoniazid has a side effect on life and further causes hepatitis⁴⁹.

Isoniazid

Also known as isonicotinyl hydrazine, is a TB treating drug.

Mechanism of action

Isoniazid metabolized in acetyl isoniazid, hydrolyzed to acetyl hydrazine in the existence of N acetyltransferase. CYP2E1 metabolizes acetyl hydrazine to the acyclic molecule which covalently binds to hepatocytes and causes hepatocytic damage⁵⁰. Isoniazid elevates

ALP, SGOT, SGPT, and bilirubin levels while lowering albumin and total protein levels⁵¹.

Procedure

Wistar rat of both gender of wt. 150-200 gm, kept in a temp. $25 \pm 2^\circ\text{C}$ and in light and dark cycle of 12 hrs, and free access to water and food before one week of experimentation. Rats were co-administered with isoniazid and rifampicin at the dose 50mg-100 mg per kg via *i.p./o.p.* for 10 days to 28 days⁵²⁻⁵⁵. A sample of blood is taken at the end to estimate the biomarker enzyme of the liver. To estimate antioxidant parameter liver is removed and histopathological studies were done.

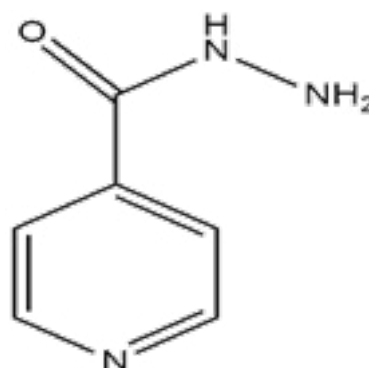


Fig. 9. Structure of Isoniazid

Table 7. Hepatotoxicity caused by Erythromycin

Animal	Dose and route	References
Rat	10mg per kg by orally	[47]

Table 8. Hepatotoxicity caused by Isoniazid

Animal	Dose	Route	References
Wistar rat	50mg-100mg perkg for 10 days to 28 days	Per oral <i>ori.p.</i>	[55]

Table 9. Hepatotoxicity caused by Radiation

Animal	Dose	References
Male Wistar Albino rats	Gamma rays were introduced in a single dose for 15 days regularly(6Gy).	[58]
Male Sprague Dawley rats	Gamma rays of 5Gy were induced for 2 days	[59]
Wistar male rat	Level 3 to 6Gy of an acute single dose for 7 days	[60]

Table 10. Hepatotoxicity caused by metal

Animal	Route and dose	References
Wistar rat(male)	80 mg per l as water for 4 weeks(HgCl_2)	[66]
Albino rat (male)	Hg-5mg per kg by injecting subcutaneously	[67,68]

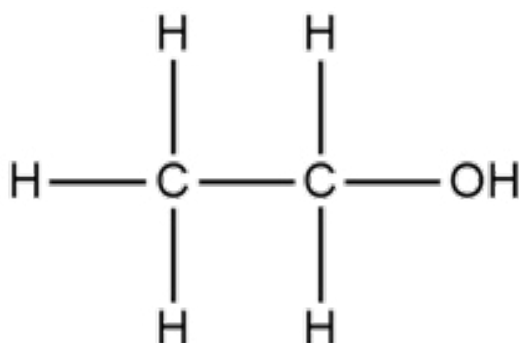


Fig. 10. Structure of Alcohol

Hepatotoxicity caused by Radiation

Radiation is a form of energy. It is produced by machines in the form of waves particles. Radiations are of two types ionizing and non-ionizing.

Mechanism of action

Acute liver injury progresses to radiation-induced liver damage. The sinusoidal endothelial cells and central vein endothelium were thought to activate the coagulation cascade in radiation exposure, resulting in fibrin build-up and clot

Table 11. Hepatotoxicity caused by Alcohol

Animal	Dose	Route	References
Wistar Albino rat (male)	7.9gm per kg	Ethanol Per oral daily for 45 days	[74]
Albino Wistar rat	2ml per 100 gm	Ethanol Per oral for 21 days	[75]
Albino Wistar rat (male)	5g per kg	Ethanol Per oral daily for 60 days	[76]
Wistar rat (female)	3.76gm per kg twice a day	Ethanol per oral for 25 days	[77]

formation in the hepatic sinusoids and central veins. The loss of centrilobular hepatic cells and reduction inside of the inner liver plate may result in liver dysfunction^{56,57}.

Procedure

Standard conditions were maintained for keeping animals, including providing a standard diet and clean water. Radiation was used to cause hepatotoxicity in the animals. An evaluation of liver biomarker enzymes is performed at the end of the experiment. It is required to remove liver tissue for assessment of antioxidant parameters (GSH, SOD, lipid peroxidation) and histopathological analysis.

Hepatotoxicity induced by Metal

In the environment, the production of toxic and carcinogenic compounds is mainly due to human activity.

Mercury

Poisoning is common among other metals. It is a transitional metal. It increases the level of ROS in the body⁶¹. Mercury has side effects or toxic effects like CVS disease, kidney or liver damage, cancer, autoimmune disease, neurobehavioral disorder, anemia, and diseases that are associated with experimental animals and human death⁶².

Mech of action

Mercury is present in different forms as it is a transitional metal; like metallic

mercury, mercurous ($\text{Hg}^{2\text{S}}^{\text{S}}$), mercury vapor (Hg), mercuric ($\text{Hg}^{\text{S}}^{\text{S}}$) are inorganic mercury⁶³. It promotes the generation of ROS. This increase in ROS increases the formation of a highly reactive radical (hydroxyl) and the formation of the lipid peroxides⁶⁴. Production of these radicals causes damage to the cell membrane and destroys it. It also inhibits the activity of the free radical SOD, GPX, and catalase⁶⁵.

Procedure

Rats of both genders were given diet and free access to water. They are taken in 12hrs a light and dark cycle. Hepatotoxicity is caused by mercury. Histopathological parameters were studied. On the last day of experimentation, animals were sedated, a sample of blood was collected, liver enzyme activity was carried out.

Alcohol

It is fermented by sugar. Alcohol is stimulant at lower doses but at a higher rate, it causes drowsiness and respiratory depression. It shows a toxic sedative effect at high doses, it has a bad effect on body organs depending on the BAC (blood alcohol conc.)^{69,70}.

Mechanism of action

As soon as alcohol leaves the small intestine, it travels to the liver where it is converted into acetate by two enzymes: (a)

by following three pathways in the liver: (a) by ADH in the cytosol; (b) by microsomal enzyme P-450; (c) by catalase such as H₂O₂. Through the generation of highly ROS, acetaldehyde may membrane damage and necrosis of cells⁷². ADH is oxidized into acetaldehyde by the liver, which is related to the NAD that reduces to NADH. As a result, NADH level got increases the activity of xanthine oxidase, which is responsible for rising superoxide levels and lowering glutathione levels in the liver⁷³.

Procedure

The male and female rats were given a standard chow diet and water in free access. We allowed them to adjust for 12 hours in a light/dark cycle before use. Alcohol is introduced to the animal for inducing toxicity Animals. Blood was collected, on the last day from retro-orbital punctures, after animals were sedated with aesthetic ether. All parameters are studied.

In-vesive model

ligation of the bile duct

Rats are more suitable for this model as they do not have a gallbladder. Extracellular deposition of matrix components occurs in the liver and this condition is characterized as liver fibrosis⁷⁸.

Mechanism of action

It is a classic secondary biliary fibrotic experimental model. Basically human liver consists of the epithelial cell which is of two types; one is biliary epithelial cell and another is hepatic cell⁷⁹. Biliary epithelial cell transports the bile acid to the hepatic cell and helps in their survival through the biliary system⁸⁰. So, obstruction in the biliary system causes cholestasis and this leads to injury in the liver and causes apoptosis by the generation of the free radical and necrosis in hepatic cells⁸¹.

Procedure

To perform this procedure, one needs to make an incision to the midline abdominal and isolate the common bile duct above the duodenum, and then the distal and proximal parts of the bile ducts are ligated. To minimize the risk of formation of cyst in bile, each lobule and the biliary duct are separately ligated. This (Ligation of the bile duct) stimulates bile duct proliferation, causing cholestasis, portal inflammation, and fibrosis, resulting in secondary cirrhosis of the biliary system and liver failure^{78,81}.

Ligation of portal-vein

Portal blood carries material that has physiological effects that result in hyperplasia and hypertrophy⁸². Early on after the ligation, inflammation, and edema accompany tissue injury. Cirrhosis and other intrinsic liver diseases are usually accompanied by portal-systemic shunting and decreased hepatic blood flow, mainly blood flow of the portal vein⁸³.

Mechanism Of action

Cirrhosis is caused by portal-systemic shunting and a reduction in hepatic, specifically blood flow of portal vein. Some pathophysiological changes seen in people with chronic liver disease are caused, at least in part, by a decrease in portal venous flow and its shunting across the liver⁸⁴.

Procedure

Incision in the upper abdomen is done. An anterior lobe PVL involves the ligation of the portal vein leading to the left side of the heart. The portal vein was held with a needle of 10-20 gauge and two to three silk ligatures were tied around it. After carefully slipping out of the ligatures, the needle opened the portal vein and the abdomen was closed before the needle was reinserted⁸⁴.

Genetic model

The role of the specific factors in fibrogenesis has been evaluated using genetically modified models. It would be reasonable to conclude that the increased fibrosis in knockout mice (KO) upon exposure to pro-fibrotic stimuli suggests that this gene product has direct and indirect pro-fibrotic and anti-fibrotic effects. In transgenic animals, exogenous genes can be introduced into the germline. This technology allows for the *in vivo* analysis of the gene function. Exogenous genes can be implanted into the germline of transgenic animals⁸⁵.

Transgenic mice TGF-1

Overexpression of TGF-1 in the liver of transgenic mice plays an important role in liver fibrogenesis by stimulating HSCs (hepatic satellite cells) that grow into the myofibroblasts and increase the production of the extracellular matrix proteins⁸⁶.

Mice/ Bcl-xL

The removal of specific anti-apoptotic gene Bcl-xL-per se induces liver fibrosis by preventing apoptosis in hepatocytes⁸⁷.

Transgenic mice PDGF

In PDGF family members overexpressing

PDGF-A, B, or C was found to upregulate TGF- β 1 and therefore result in liver fibrogenesis^{88,89}.

Mice/Abcb4(Mdr2/mice)

The removal of phospholipid transporter from bile causes chronic cholangitis and severe biliary fibrosis in ABCB4-KO mice. This results in intoxication-based liver and bile duct damage⁹⁰.

CONCLUSION

Liver injury can be caused by many reasons it can be genetic, by the generation of the free radical, by metal by drug most commonly, or by radiation which will lead to pathological changes in body. Although significant progress has been made in the last few years, there is clearly a need to further improve insight into the molecular mechanisms of liver injury and cell death in all experimental models. In this review, our main aim is on animal models for hepatotoxicity and pathological changes resulting in hepatotoxicity. There are still huge gaps in knowledge concerning the animal model, in understanding the diseases in human and in the translation of the model to the human disease.

Conflict of Interest

There is no conflict of interest.

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