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Mechanism of detoxification

Sunny Nain

College of Pharmacy, LPU, Punjab, India [Email: sunny.nain@gmail.com]

The liver plays a vital role in the metabolism of many exogenous and endogenous substances which are usually excreted in the urine or bile; however, lipid-soluble compounds usually accumulate in the body and affect cellular function unless they are easily excreted out. There are several enzyme systems involved in the biochemical transformations. There are two major types of reactions that occur in the liver in the presence of exogenous substances.

Phase I reaction:

Phase I reactions involve chemical modification of groups by oxidation, reduction, hydroxylation, sulfonation and dealkylation. Various enzymes including mixed oxidases, cytochromes b5 and P-450, and the glutathione S-acyltransferases are involved in biochemical transformations that usually lead to inactivation of drugs, such as barbiturates and benzodiazepines. There are examples where activation of drugs in the liver also takes place. Cortisone and prednisone are activated through biochemical transformation to cortisol and prednisolone, which are more potent than their parent compounds. In some cases, a nontoxic compound is transformed into a toxic one, as is evident from the metabolism of isoniazid and paracetamol. During metabolism, carcinogenic hydrocarbons become highly activated by the formation of epoxide intermediates in the liver, while other carcinogens are detoxified. The activity of phase I reactions may also change with aging.4

Phase II reaction:

Phase II reactions involve the conversion of exogenous substances on those metabolized via Phase I reactions into glucuronide, sulfate, acetyl, taurine or glycine derivatives to turn lipophilic substances into water-soluble derivatives that are excreted in the bile or urine. The general characteristic of phase II reactions is the conjugation catalyzed by microsomal uridine diphosphate glucuronyltransferases to glucuronide derivatives, which are pharmacologically inactive.

Disordered liver architecture can also affect hepatic drug clearance. A decrease in the function of microsomal enzymes for phase I and phase II reactions reduces the rate of drug activation and elimination.4

Some agents exert their hepatotoxic effects through the metabolic pathways that are responsible for drug detoxification. For example, the toxicity of paracetamol−a frequently used drug−is believed to be caused by the formation of a free radical intermediate N-acetylimidoquinone during detoxification processes that inactivate many enzymes and proteins by binding irreversibly to their sulfhydryl groups. Overdose of paracetamol increases the concentration of free radicals, which deplete the glutathione levels of the hepatocytes and thereby lead to inactivation of cellular proteins and widespread hepatocellular necrosis. The toxic effect that arises from overdose of paracetamol may be prevented by early administration of N-acetylcysteine.4

Another mechanism by which mixed function, oxidase-dependent biotransformations produce liver cell injury is a result of the formation of activated oxygen species. The cytochrome P-450 system produces hydrogen peroxide from the dismutation of superoxide anions. The oxidative stress imposed by the formation of O2 and H2O2 may offer an alternative to covalent binding as an explanation of biological activity.4

The destruction of cultured hepatocytes by aryl halides is accompanied by peroxidation of cellular lipids, followed by accumulation of malondialdehyde and the appearance of conjugated dienes in cellular phospholipids. The antioxidant N,N′-diphenyl-p-phenylene diamine reduces lipid peroxidation.

Reference:

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