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ORIGINAL ARTICLE

XENOBIOTICS AND WE

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Abstract:

In the modern era of technical and industrial revolution; by and by, human race has become vulnerable to many foreign chemicals; to exemplify – various drugs, food additives, industrial toxins, polychlorinated biphenyls (PCBs) and insecticides. A xenobiotic is a chemical which is found in an organism but which is not normally produced or expected to be present in it (Prefix 'xeno-' means foreign or other). If one understands what actually xenobiotic is and how it affects living cells, one can think of preventing this notorious actions of xenobiotics. Study of metabolism of xenobiotics is a very significant entity of certain scientific-disciplines viz pharmacology and therapeutics, pharmacy and toxicology.

KEYWORDS:

technical and industrial revolution , xenobiotic , foreign chemicals.

INTRODUCTION

This knowledge will also help us in effective management of cancers. There are certain Drug metabolizing enzymes (DMEs) which play a central role in the metabolism, detoxification and elimination of not only xenobiotics but also certain endobiotics. Thus they play a significant role in the protection of body1. DMEs include phase I, phase II metabolizing enzymes and phase III transporters. These are found in abundant amount and remain at certain baseline level but can be induced to elevated level whenever they are exposed to xenobiotics[1,2]. Details of all these three phases of metabolism are as follows-

Phase I

There are several enzymes involved in phase I reactions, out of which, Cytochrome P450 (CYPs; P450s) is most important of and it causes monooxygenation. It is a superfamily of microsomal enzymes,

further subdivided into families and subfamilies based on their amino acid sequences. CYPs are found abundantly in the liver, GIT, lung and kidney etc [1,2,3,4,5]. CYPs bring about detoxification and/ or bioactivation of a galore of xenobiotics. They also cause fictionalization reactions (e.g. N- and O-dealkylations, aliphatic and aromatic hydroxylation, N- and S- oxidations and deamination). Phase I reactions usually involve hydrolysis, reduction and oxidation reactions. Hydrolysis is done by esterase, peptidase and epoxide hydrolase. These enzymes are located in microsomes, cytosol and lysosomes. Reduction reactions are of various types including carbonyl reduction, disulfide reduction, sulfoxide reduction and reductive dehalogenations. Enzymes involved in reduction processes are located in microsomes and cytosol. Oxidation reactions are done by various oxidase enzymes like aldehyde oxidase, xanthine oxidase, di-amine oxidase etc. These enzymes are located in mitochondria, microsomes and cytosol.

Phase II

'Transferase' enzymes perform conjugating reactions and catalyze phase II biotransformation. Glucuronidation, sulfation, methylation, acetylation, glutathione-conjugation and amino acid-conjugation are some important examples of these reactions. These enzymes have many superfamilies further subdivided into families and subfamilies[6-10]. Phase II reactions run in concert with phase I to metabolize, detoxify and sometimes bioactivate xenobiotic substrates. Besides all these, genetic polymorphisms in all these genes are also encountered resulting into increased incidences of cancers and other toxicities derived from chemical and drug exposures. Main enzymatic processes involved in phase II synthetic reactions are-glucuronide conjugation (in microsomes), glutathione conjugation (in cytosol and microsomes), amino acid conjugation (in mitochondria and microsomes). Main drugs undergoing glucuronide conjugations are morphine, diclofenac, amitriptyline, thyroxine, acetaminophen, chloramphenicol, ethyl alcohol, estradiol and estrone mainly involve sulfate conjugation. Methyl conjugation is mainly utilized by arsenic compounds, nicotine, levodopa and cocaine. Isoniazid and sulfa-drugs are acetylated to excrete them. Very few drugs; like ethacrynic acid, diethyl maleate undergo glutathione conjugation.

Transporters governing Phase III –

Several tissues including liver, intestine, kidney and brain contain these transporters viz P-glycoprotein (P-gp), multidrug resistance associated protein (MRP)[12] and organic anion transporting polypeptide 2 (OATP2)[13]. They play crucial roles in absorption, distribution and excretion of xenobiotics, as well as create a formidable barrier against xenobiotics penetration[11,14,15]. P-gp and MRP are called ATP binding cassette (ABC) transporters[15]. ABC transporters are one of the largest superfamilies of proteins. There are several types of MRP which perform distinct functions; for instance, MRP2-mediated transport leads to increased excretion in bile, whereas MRP1 and MRP3-mediated transports into blood lead to increased excretion in the urine. Organic anion transporting polypeptide family includes Organic anion transporting polypeptide 2 (OATP2; SLC21A5). It mediates sodium- and ATP independent transport of various endo and exogenous compounds. P-gp, MRP and OATP2, all are found on the brush-border membrane of the intestinal enterocytes. Here they cause excretion of substrates (which also include xenobiotics) into lumen, thereby potentially limiting the net absorption of xenobiotics [12, 14, 15]. Regulation-process of gene expression of various phase I, phase II DMEs and phase III transporters significantly affect metabolism, pharmacokinetics/dynamics, toxicokinetics/dynamics and elimination of xenobiotics, as well as their ability in the protection of our body from toxic substances and their metabolites[2,4].

VARIOUS EFFECTS OF XENOBIOTICS ON PHYSIOLOGY

Xenobiotics have potential to harm the living entity directly or indirectly by dysregulating various physiological processes. Dysregulation of normal physiology produces number of ailments. Some of them are as follows-

HEPATITIS-

Hepatitis is characterized by progressive liver inflammation that may progress to advanced damage including fibrosis. The inflammation consists of both cell-mediated cytotoxicity by infiltrating lymphocytes and the production of autoantibodies. Autoantibodies specific for metabolizing enzymes of phase I and phase 2 can be found in patients with either type 1 or type 2 hepatitis. This has led to the

suggestion that hepatitis can be triggered by some compounds that perturb these enzymes. Liver is most common site for metabolism of ingested pharmaceuticals and xenobiotics into more active; and in some cases toxic, breakdown products. Cytochrome P450s (CYPs) account for approximately 2-4% of total liver protein. In humans the most abundant CYP isotype is CYP3A (29%) followed by CYP2C (18%), CYP1A2 (13%) and CYP2E1 (7%). CYP2D6 is found in small amounts (<2%), but accounts for the metabolism of almost 30% of all drugs[16] . Many xenobiotics including therapeutic products have been found to be associated with hepatitis[17-20]. In patients suffering from halothane-induced hepatitis autoantibodies against CYP2E1 were found [21]; and in patients with dihydralazine-induced or tienilic acid-induced hepatitis, anti-CYPlA2 antibodies and anti-CYP2C9 antibodies have been found, respectively[22]. Xenobiotic exposure can be either occupational or environmental.

IMMUNE DYSREGULATION-

By directly affecting the immune system; xenobiotics can lead to decreased resistance to infections or tumors, alter the course of autoimmunity or induce hypersensitivity reactions. Most of the data about immunotoxic agents such as dioxin, polychlorinated biphenyls, immunotherapeutic drugs etc. are derived mainly from animal research such as those on mice and rats, although a few biomarkers exist that provide specific information about immunotoxicity in humans[23-25]. Number of surrogate markers suggestive of immunotoxicity are- lymphocyte count, immunoglobulin concentration in serum, anti A and anti B blood group antigen, C-reactive protein and complement system components[26].

MUTATION-

Incidence of a carcinogenic process has been shown to correlate with the human DNA adduct formation (covalent modification of DNA with chemical carcinogens) which is a promising biomarker for enlightening the molecular epidemiology of cancer.[27] There is a sequence of events that occurs after the first interaction of a xenobiotic with DNA and consequent mutation: 1ststage is the formation of adducts; next stage may be secondary modifications of DNA, such as strand breakage or an increase in the rate of DNA repair; and 3rd stage is reached when the structural disruptions in the DNA become fixed and the affected cells often show altered function. Finally, when the cells divide, damage caused by xenobiotics can lead to DNA mutation and consequent alterations in the descent[28,29]. Some toxic compounds capable of forming human DNA adducts are polycyclic aromatic hydrocarbons, aromatic amines, heterocyclic amines, mycotoxins (aflatoxin B1, ochratoxin A), chemotherapeutic agents (cisplatin, procarbazine, dacarbazine) and ultravilolet light.[30,31] The aberrant expression of genes that encode proteins involved in cellular growth is associated with the development of many tumors related to xenobiotics. This aberrant expression can involve a quantitative difference such as over-expression of the protein and a qualitative difference such as expression of a mutant form of the protein.

Biomarkers of gene expression[32]

Platelet-derived growth factor (PDGF): Breast cancer, various other carcinomas, sarcomas, lymphomas, lung fibrosis, pneumoconiosis, atherosclerosis; Transforming growth factor-α (TGF-α): Breast cancer, various other carcinomas and pneumoconiosis; Transforming growth factor β (TGF-β): liver cancer, bladder cancer, breast cancer, leukaemia, liver and lung fibroses and pneumoconiosis; Fibroblast growth factor (FGF): renal cancer and bladder cancer, etc; Insulin-like growth factor (IGF): bladder cancer, ovarian cancer, hepatitis and cirrhosis; Hepatocyte growth factor (HGF): liver cancer, hepatitis and cirrhosis; Transmembrane growth factor receptors (encoded by the erbB-2 oncogene): cancers of bladder, ovary, liver and lung etc; Epidermal growth factor receptor (EGFR, encoded by the c-erB-1 oncogene): lung and some other cancers; Membrane-associated G proteins or p21 (encoded by the ras oncogene): lung cancer, colon cancer, liver angiosarcoma etc; Nuclear DNA-binding protein (encoded by the myc oncogene): cancers of lung and bladder; Nuclear phosphoprotein p53 (encoded by the tumour-suppressor gene p53): cancers of liver, breast, lung, colon and lymphoma.

OXIDATIVE DAMAGE-

Free radical induced oxidative damage may be caused by certain contaminants [e.g. polycyclic aromatic hydrocarbons (PAHs), halogenated aromatic hydrocarbons, heavy metals, selenium, pesticides and industrial solvents]. To cope with this stress, antioxidant systems within the body may get activated.

There is also modification of cellular macromolecules and tissue damage. For various xenobiotics, these modifications in antioxidant systems and macromolecules may serve as biomarkers. Antioxidant protective systems include oxidized glutathione/reduced glutathione, glutathione reductase, catalase, superoxide dismutase and peroxidase, ascorbate and α-tocopherol. Lipids, proteins and nucleic acids are some macromolecules that may be affected by free-radical damage.

To summarize, our body is exposed to number of xenobiotics which may be having high potential to damage living tissues. Xenobiotics exposure is further increased due to overuse of synthetic materials including drugs and food products. Body behaves adversely against the substances which are unfamiliar and synthetic. This may be the possible reason for the mutagenicity, carcinogenicity shown by number of synthetic products. Natural products are handled by the body in more favorable way. This may be keypoint in searching the drug molecules from the natural sources rather than from the synthetic ones. Natural ways of prevention of disease is far safer than being treated by synthetic products. Xenobiotic exposure can be curtailed by reducing the use of insecticides, pesticides, detergents, colouring agents etc. In the end, a flowchart summarizing the various potential damaging effects of xenobiotics is given-

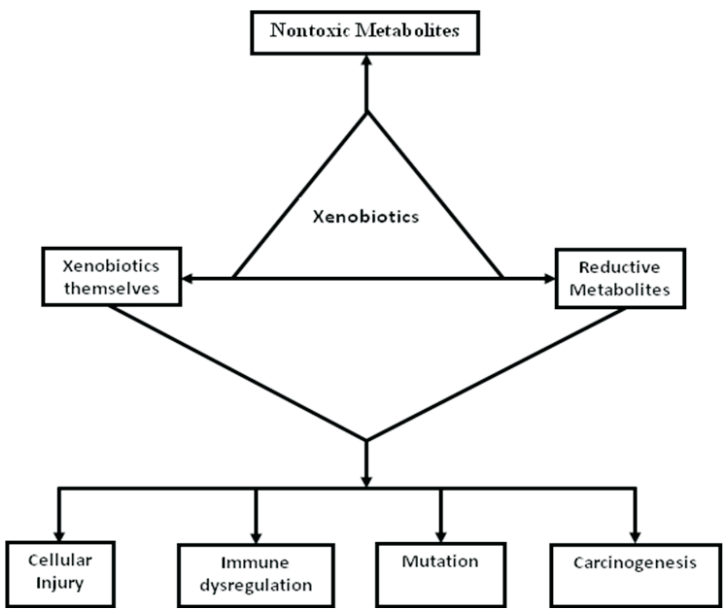

Figure: Xenobiotic induced cell injury

CONCLUSION-

Xenobiotics are certain chemical compounds which are foreign to the human body. For example, these may be drugs, additives in food and pollutants in environment. Their metabolism takes place mainly in three phases. Phase 1 is actually a hydroxylation reaction in which there is a momentous involvement of various types of monooxygenases/ cytochrome P450s which catalyze this phase. While, in phase 2, conjugation of these hydroxylated species with various hydrophilic compounds is done; examples of these reactions are glucuronidation, sulfation, methylation, acetylation, glutathione-conjugation and amino acid-conjugation. Now, in phase 3, various transporters play important roles in absorption, distribution and excretion of xenobiotics, as well as create a strong barrier against Xenobiotics-penetration. The definitive motive of these reactions is to convert these xenobiotics from lipophilic to hydrophilic form so that these may be easily excreted from the body, otherwise xenobiotics can produce various detrimental effects in terms of pharmacologic and immunologic responses and which may also result in toxicity and cancers.

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