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Drug/Xenobiotic-Metabolism, Disposition and Toxicity in Malnutrition

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ABSTRACT

The role of malnutrition and diet in general on bioprocess, which govern the fate of drug/xenobiotic in the body only just beginning to be understood. Absorption, protein binding distribution, bio-transformation and renal elimination of xenobiotics/drugs are all affected by altered states of nutrition. As such, evaluation of nutritional status is highly relevant prior to prolonged drug thereby especially with drugs having narrow safety margin.

1. INTRODUCTION

In recent years, the impact of environment on man is gaining a wide recognition as we are exposed to a wide variety of chemicals foreign to the body. Toxicology is a science which deals with qualitative and quantitative aspects of environmental effects on biological tissues and their mechanisms. The implications of toxicity or influence of xenobiotics in terms of dose and duration of exposure are explored with regard to absorption, distribution, elimination and action of toxicants in human body. Thus the interaction of chemicals with the biological system is a complex phenomenon and is ultimately an expression of the interplay between the environment, the host and chemical substance. The three important phases namely the exposure phase (Pharmaceutical), the toxicokinetic phase (Pharmacokinetic) and the toxicodynamic phase (Pharmacodynamic) will directly determine the outcome of drug response or toxicity manifestations (Fig. 1).

A number of internal and external factors can modify these phases.[1,2] The physico-chemical prospective of xenobiotics/drugs and the physiological and pathological variables of the host will determine the entrance and the exit of xenobiotic drug from the body. The ultimate outcome of the drug/toxicant is therefore a summation of

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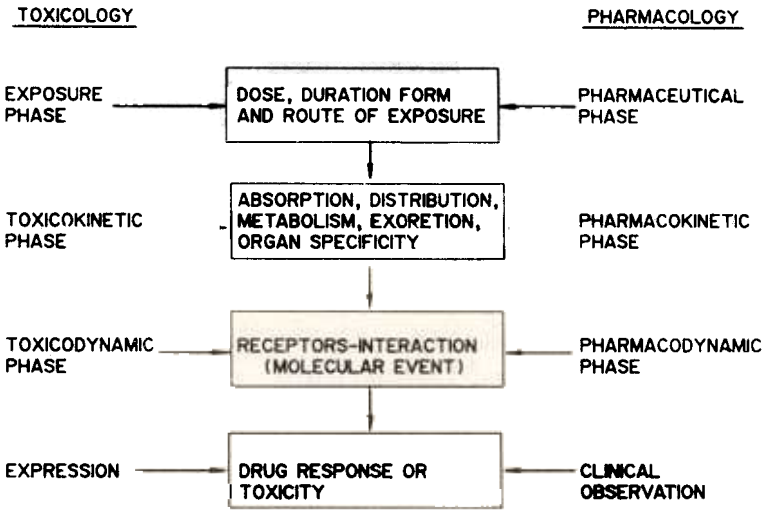

Figure 1. Interaction between chemicals and human body.

effects observed as a therapeutic/toxic process/diseases. A number of factors as shown in Table 1 are known to be involved in this process.[3]

Table 1. Toxicity determinants

1 Site of entry	6 Elimination profile
2 Membrane barriers	7 Dose related effects
3 Distribution and tissue specificity	8 Combination factors
4 Binding characters	9 Inducing/inhibiting potency
5 Metabolic profile	10 Pool location, size, reaction intermediates

Food is a prerequisite for existence and good health of man, and is an important link between man and his environment. Nutrition associated toxicity problems are both of basic and applied interest and a topic of current concern.[4] The physical, physiological and pathological interactions between diet and xenobiotics influence nutritional processes and alter drug/xenobiotic metabolism, disposition, potency and toxicity. However, food in addition to supplying nutrients, may also serve as vehicle for toxins. The toxicants may be naturally occurring toxin (inorganic substances, toxins of microbial origin, plant products or organic compounds) or food additives such as preservatives, colours, sweeteners, flavouring agents etc. In addition, food contaminants such as pesticide and herbicide residues, water and other pollutants are further sources of toxicants. Drugs or pharmaceutical products, which are used to cure diseases are also xenobiotics with both therapeutic/toxic potentials.

Hence it is necessary to consider the role of nutrients in xenobiotic/drug metabolism and disposition and the effect of xenobiotics on nutrient absorption, metabolism and excretion.

2. MALNUTRITION

For nutritionists and other professionals in health, drug disposition, nutrition-drug/xenobiotic interaction has become a challenge and a responsibility. The role of malnutrition and diet in general on bioprocesses which govern the fate of drug/xenobiotic in the body are only just beginning to be understood.[5] The nutrients in the diet and the nutritional status can considerably alter these processes and modifying amount of drug/toxicant available for action.

The major nutritional disorders which are widely prevalent in all developing countries are protein energy malnutrition (PEM), vitamin A deficiency, iron deficiency anaemia, vitamin B complex deficiency and iodine deficiency. They affect all age groups and more so of poorer segments of the population. However, the repercussions are strongest in children and pregnant or lactating women.[6]

A number of pathophysiological changes are encountered in nutrient deficient states. They affect gastrointestinal tracts, body composition and fluids, plasma/tissue proteins, organ functions such as liver and kidney and heart. In addition a host of endocrinal and metabolic changes occur,[7] which have a great potential to alter xenobiotic absorption, distribution, binding, metabolism and excretion. The alterations and the clinical significance are briefly considered here.

2.1 Absorption of Toxicants/Drugs

Most xenobiotics including drugs are lipophilic substances. They are either absorbed passively or actively along the mucous membrane. Along the food chain, the load of pollutants invariably increases. The uptake of xenobiotics is invariably higher from the gastrointestinal tract, in which the concentration is high than from the environment. However, it is possible that due to alterations in the mucous membrane and gastrointestinal functions, absorption of xenobiotics may decrease. Drugs such as antibiotics and nutrients absorption such as iron, vitamin B_{12} are known to go down in malnutrition.[8] Very little is known about xenobiotic absorption in malnourished human host. However, several studies indicate that food *per se* can either increase or decrease absorption of drugs.[9]

2.2 Binding and Distribution

Most xenobiotics are transported in blood bound to proteins, albumin and globulin.[10] The extent of binding varies according to the chemical nature of drugs/xenobiotics and its affinity for the protein. Since protein-drug complexes cannot cross tissue barrier, the free drug/xenobiotics is an important determinant of both toxicokinetic (Pharmacokinetic) or toxicodynamic (Pharmacodynamic) effect of xenobiotics.

The qualitative and quantitative changes in food can directly influence the plasma protein profile and the binding of xenobiotics. Many endogenous substrates such as free fatty acids, bilirubin, steroids, thyroid hormones, tryptophan, histamines and uric acid bind to albumin. A significant reduction in binding of several drugs has been

observed in malnutrition both in adults and children.[11] Free cortisol levels are known to be elevated in malnutrition.[12]

The significance of drug protein binding is often debated. The alterations in binding can however lead to variabilities in other pharmacokinetic parameters. The organ clearances of drugs and xenobiotics will be ultimately determined by unbound free fraction. If the free drug clearance is low, relative to the organ blood flow the clearance is always dependent on the binding properties. Therefore the xenobiotic and drug clearances will be altered depending upon the protein-drug/toxicant interaction. If free drug concentration are higher, elevation in drug/toxicant responses for non restrictive clearance of drugs have been demonstrated.[13]

The uptake of the xenobiotics and drugs by various organs and tissues will depend upon the organs or tissues specificity/affinity as well as receptor drug interactions. Both proteins and fats in the body are directly determined by nutrients and food components. The drug distribution is significantly altered in obesity. In the malnourished human host there is a significant reduction in adipose mass as well as lean body mass which therefore would alter the distribution characters. The distribution into adipose tissue of lipid soluble substances such as pesticide residues and drugs like tetracycline will automatically be reduced.[14] The clinical implications for such reductions would therefore be of significance and the responses would vary depending upon the extent of reduction as well as the clearance characters of the drug. Concentration of lipid soluble substances will increase at target tissues.

2.3 Biotransformations

Diet and nutrition have been identified as major factors which influence the chemical transformations of drugs and other xenobiotics in experimental situations.[15-18] The effects of foreign compounds in general are regulated by their metabolism by enzymes located in the endoplasmic reticulum in liver and other tissues such as lungs, kidneys, intestine, skin, brain, adrenals, blood cells and placenta. The liver, however, is by far the most important organ for the metabolism of foreign compounds. The biotransformation of environmental chemicals involves Phase I (oxidation, reduction, hydrolysis) and Phase II (conjugation) processes mediated by mixed function oxidase and conjugation enzymes. The components of the multienzyme system are haemoprotein cytochrome P450, a flavoprotein-NADPH cytochrome P450 reductase and lipid phosphatidyl choline.

The enzyme system has a wide substrate specificity. The balance between intracellular reactions that result in activation of a specific compound to a more reactive form and those detoxification reactions that make the compound less reactive determines the extent of cellular damage and toxicity expression. The enzyme activity *per se* is an expression of interplay of genetic, environmental, physiological and pathological factors which directly determine drug or xenobiotic activity and toxicity.

A number of nutrients are known to be involved in the functioning of these enzymes (Fig. 2), either participate in the overall functioning or act as cofactors or as substrates in the enzyme activity or are involved in membrane stability. In

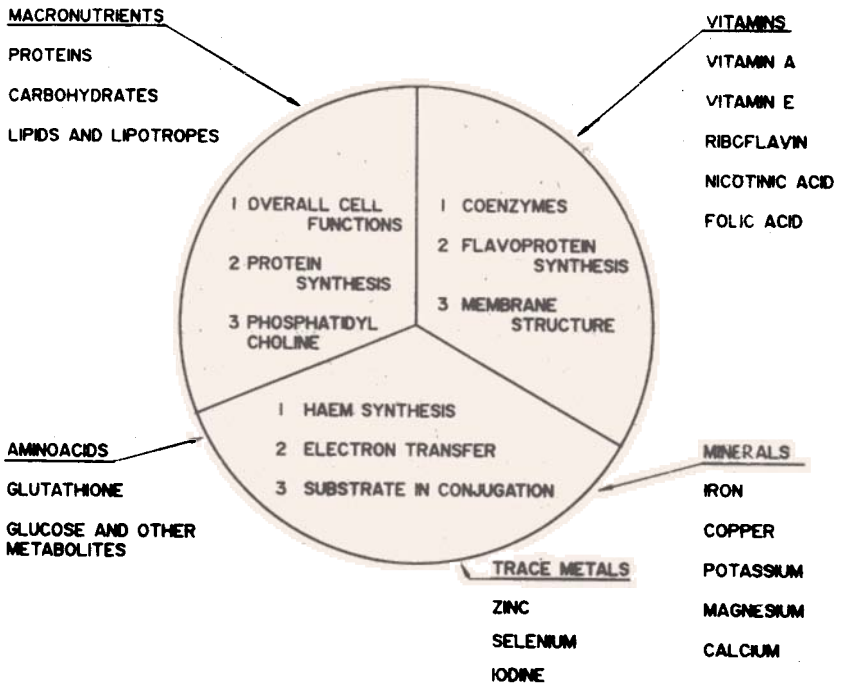

Figure 2. Nutrients and biotransformations.

experimental situation, nutritional stress has often been shown to alter the activity of these enzymes. These alterations have been shown to be dependent on species, stress, age, sex, type and degree and duration of nutritional deprivation and also on the type of substrates being investigated.[4,19] In general, all specific deficiencies except those of thiamine and iron, decrease metabolism of drugs.[16,20] Oxidative metabolism is often diminished and also the conjugations are decreased in starvation. In chronic semi-starvation, mixed function oxidase activity is higher with no change or decrease in conjugations (Table 2). Protein deficiency is known to decrease the mixed function

Table 2. Nutritional status and enzyme function

Condition	Mixed function oxidase	Glucuronyl transferase	Glucuronyl	Glutathione-S-transferase
Starvation				
Acute	↓	↓	↓	↓
Chronic (semi)	↑	↓ No change	No change	↓
Protein deficiency (5%)	↓	↑	↓	↓
Carbohydrates (glucose, sucrose, fructose)	↓	↓	No change	↓
Lipids/Lipotropes	↓	↓		

oxidase activity with variable effect on conjugations. Lipid deficiency in general decreases the enzyme levels. The ability of animal studies of nutritional adequacy or inadequacy to predict pharmacological effects in man is ambiguous. Animal studies cannot always be extrapolated to humans and have to be viewed with a great caution.[21] Single nutrient deficiency and excess do not exist in the population. The nature of the nutritional deprivation both in terms of duration and degree are not comparable to human situations.

Therefore, attempts have been made to obtain information in human subjects in the naturally existing situations in adults[7,8,20,21] and in children[22,23], as well as in experimental situations where dietary modifications have been attempted.[24,25] The clearance of drugs are decreased in severe cases of malnutrition such as kwashiorkor, marasmus and nutritional oedema. Xenobiotics have a tendency to accumulate due to decreased clearance of drugs such as phenazone, chloramphenicol, chloroquine, paracetamol, phenylbutazone, isoniazid and sulphadiazine in children.[21,26] In adults, however, clearance of drugs depends upon the severity of the nutritional status. The oxidative metabolism of drugs is enhanced either due to nutritional/environmental stress in cases of mild and moderate malnourished subjects.[27] It has also been observed that in children with malnutrition, vitamin D hydroxylations are comparable to that of normal subjects.[28] On the other hand, nutrition effects on conjugations are variable. Metabolism of contraceptive steroids are found to be faster in undernourished women.[29,30] The diminution and endogenous estradiol activity due to faster conversion of steroids is also documented.[31] On the other hand, paranitrophenol conjugation is lower in undernourished subjects.[27]

Metabolic experiments in adults on varying energy and protein intake indicate that very low protein intake resulting in negative nitrogen balance decreases drug metabolism whereas on adequate calories minor differences in protein intake of the order of 5-10 per cent do not have any significant impact[32]. Protein in the diet contributes to 20-40 per cent of energy results in stimulation of enzymes leading to faster clearance of drugs and xenobiotics.[24] In energy deficiency recent observation indicate no change in drug clearance whereas in severe protein deficiency clearances decreased.[33]

In addition to the nutrients, non-nutrient components in the diet are also known to significantly enhance or reduce drug metabolism and clearance.[25] Several studies indicate that plant chemicals such as indoles, flavones, phenols and isothiocyanates can stimulate drug metabolism in man. Cruciferous vegetables such as cabbage and brussel sprouts increase clearance of antipyrine and theophylline.[34] Though experimental evidences are available on either induction or inhibition, no data is available to indicate that the dietary inducers and inhibitors significantly alter the therapeutic and toxic effects of drugs and xenobiotics.[35] However, strong inducers such as drugs *per se* are known to result in important drug-drug interactions which are of therapeutic significance.

In addition to macro nutrients, micro nutrients deficiency needs to be considered in human population. Very little information is available in humans. Iron deficiency in humans have been shown to increase drug clearance. Zinc deficiency, on the other

hand is associated with decrease enzyme activity and clearance of drugs. Drug metabolism in general has not been explored in depth in micro nutrient deficiency.

2.4 Renal Elimination of Drugs

Urinary excretion is the primary route of elimination for water soluble drugs and their metabolism. Controversial reports exist on kidney function in malnutrition. The recent data on renal function reserve indicate that kidney function can be related to protein intake.[36] Diet induced changes in pH and ionisation of drugs will also alter renal elimination of drugs. Studies conducted on drugs which are excreted by kidney in severe malnutrition indicate that the clearance is decreased by renal route. On the other hand in mild and moderate forms, kidney function is in tact and drug clearances are enhanced due to alterations in binding and availability of free drugs.

3. PHARMACODYNAMICS : RECEPTORS, DRUG RESPONSE AND TOXICITY

Drug receptor interactions are difficult to evaluate and information on magnitude of response is limited. Studies on hormonal receptors indicate that nutritional status alters receptor sensitivity.[37] Such alterations may have repercussions not only on clinical response but also determine susceptibility to organ damage. Higher requirements for propranolol and prazosine has been demonstrated in African Negro patients probably indicating altered response.[38,39] Theophylline responses have been noted to be better in children who are on very low protein intake.[40]

Studies in animals indicate that nutritional status is an important determinant of drug toxicities.[41] The various permutations are shown in Table 3. Anthracycline has been associated with cardiomyopathy more in malnourished children. Acetaminophen toxicity is also documented to be higher in malnutrition. Hypoalbuminaemia is often associated with more toxic reactions.[42] Recently the subject of toxicity through metabolic activation is widely studied. Our results in mild and moderate undernourished adults indicate that the mixed function oxidase activity is in an induced state and therefore the undernourished are more at risk of developing toxic metabolites.[27] It is also interesting to observe that aflatoxin metabolites are higher in children with kwashiorkor.[43] The deleterious effects of exposure to high levels of such toxic compounds in the presence of undernutrition may precipitate toxicity at early stages and result in higher incidence of diseases associated with such toxicity. However, it is important to remember that the toxicological significance of induction differs from substrate to substrate, the quantum of induction and tissues in which the enzymes are induced. Inducers and inhibitors can have significant effect on the toxic and carcinogenic effect of chemicals.[44] Nutritional modulations of the inducing and inhibiting effect of chemical may also make it either more or less susceptible for tumour production. It is possible that the cycle of altering food shortage and food sufficiency which are encountered in poor communities may have consequences beyond the obvious ways of hunger and brief nutritional deficit.[45] However based on the incidence of human cancers in relation to diet[46] and experimental studies in animals[47] and the effect of nutrients on carcinogen metabolism, it may be surmised that certain diseases such as cancer can be related to the effect of nutrients on drug metabolising enzymes.[48]

4. CONCLUSION

It is evident from available literature that a number of drug/xenobiotic nutrient interactions can result in altered response/toxicity which are of clinical relevance. Hence, it is necessary to evaluate the nutritional status before instituting drug therapy particularly for prolonged periods of time. Dietary modifications may be called for adequate therapeutic response. Clinical and epidemiological data have yet to be explored in depth in malnourished subjects particularly on efficacy, and acute and chronic toxicity of drugs. Drugs with narrow margin of safety with dose dependent kinetics and with severe toxic reactions need to be evaluated in malnutrition.

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