General Toxicology

Host & Environmental Factors

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Objective of this lecture is to:

Determine host & environmental factors affecting toxicity.

Host & environmental factors affecting toxicity:

Among factors that influence toxicity are:

- Host, &
- Environmental factors.

Host factors:

- Genetics
- Gender
- State of health
- Age & maturity, &
- Nutritional state & dietary factors.

Genetics:

- Pharmacogenetics describes the differences in an individual's response to drugs & chemicals that are related hereditary influences due to genetic polymorphism.

- Examples:
- Succinylcholine is a skeletal muscle relaxant that is often administered during the induction of general anesthesia.

  The toxicologic problem arises because of the presence of an atypical pseudocholinesterase in a segment of the population.

This would predispose them to a prolonged & life-threatening paralysis of respiratory muscles because the initial detoxifying step in succinylcholine metabolism is hampered.

- Another example: individuals with erythrocytic glucose 6-phosphate dehydrogenase (G6PD) deficiency are at special risk of toxicity to oxidizing agents, such as naphthalene, & sulfonamides.

  When red blood cells (RBCs) are exposed to oxidizing agents, reduced glutathione (GSH) protects them from cellular injury & hemolysis.

Regeneration of glutathione to its reduced form (GSH) again requires reduced nicotinamide adenine dinucleotide phosphate (NADPH) & glutathione reductase (Figure 1).

Obviously, when G6PD is deficient, RBCs are unable to generate NADPH &, therefore, GSH function is impaired.

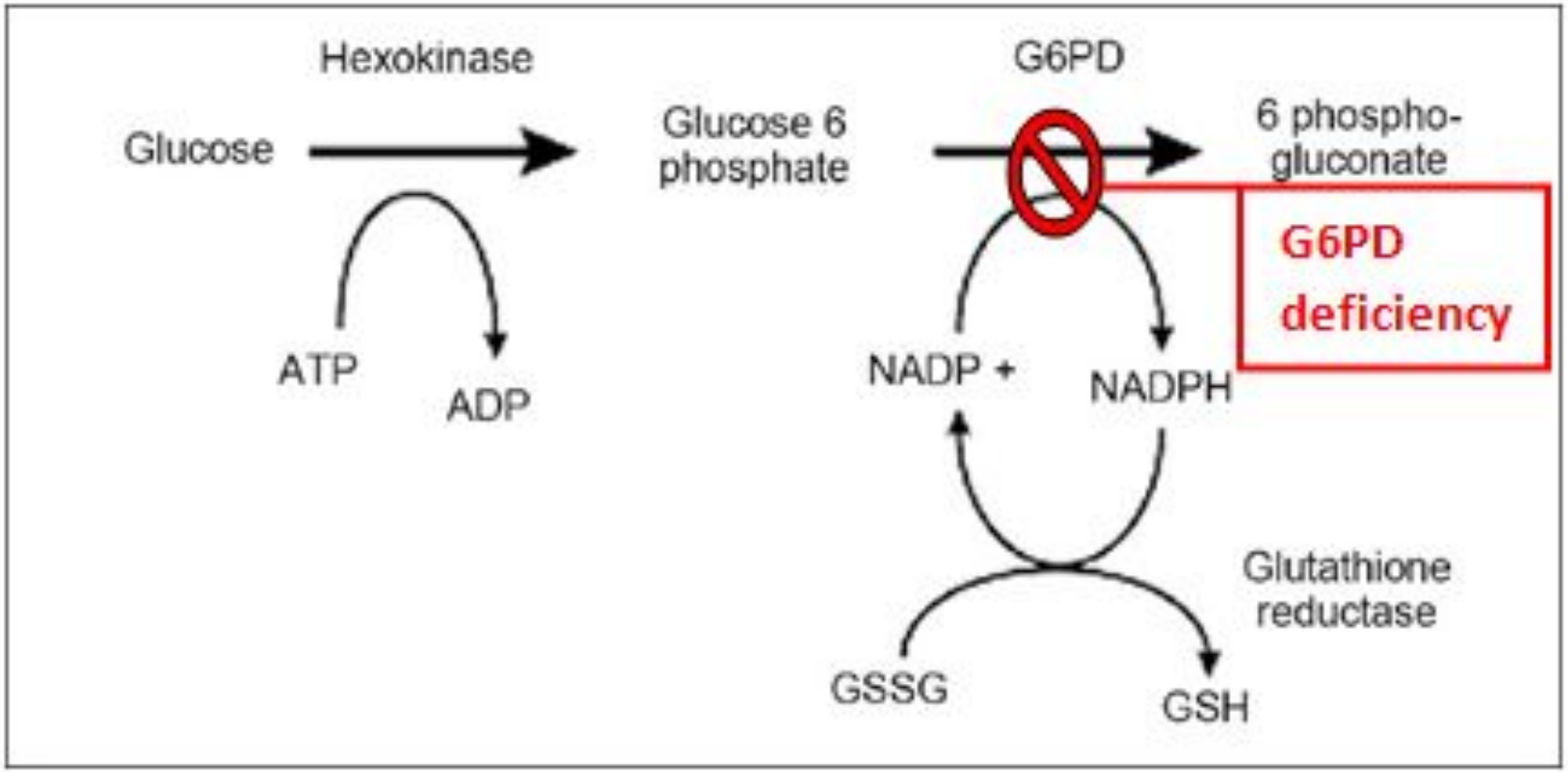

Figure 1. **The role of glucose 6-phosphate dehydrogenase (G6PD) in protection against oxidizing agents in red blood cells.**

Gender:

- There are differences in drug & chemical responses between men & women.

- Examples:
- Some studies report a sex-related difference in absorption of erythromycin, resulting in less drug being absorbed by women after oral administration.

- Another example, bioavailability of ethanol is greater in women than in men.
  This is associated with decreased gastric alcohol dehydrogenase activity in women, which contributes to reduced gastric oxidation of ethanol.

State of health:

- The presence of hepatic or renal disease may significantly affect the pharmacokinetics & outcome of exposure to a particular toxicant.

- Disease states that cause diarrhea or constipation may decrease or increase the time of contact between chemical & absorptive sites &, thus, reduce or enhance absorption.

Age & maturity:

- Anticipated toxic effects are based on individuals who are either too young or too old.

- The majority of accidental poisonings in fact occurs in persons less than 5 years of age.

- An example of the effect of age & maturity on toxicity is the chloramphenicol-induced gray baby syndrome occurring in infants.

Chloramphenicol is normally metabolized & excreted largely as a glucuronide conjugate.

Infants are unable to metabolize chloramphenicol because their hepatic microsomal enzyme system was not fully developed. Consequently, toxic concentrations of chloramphenicol would be reached after only a few doses.

- In geriatric patients, the toxic effects of drugs & chemicals may be complicated by decreased hepatic & renal function.

  These factors may alter the metabolism or excretion of toxic agents.

Nutritional state & dietary factors:

- In general, higher blood concentrations are achieved when drugs are taken on an empty as opposed to a full stomach.

- Certain food may significantly increase or decrease drug absorption. For example, calcium may bind to tetracycline & reduce its absorption.

- Some foods can actually increase the toxicity of certain drugs by means other than influencing their absorption.
  An excellent example are those foods that are rich in the pressor amine, tyramine.
  If one of these foods is ingested while an individual is taking a monoamine oxidase-inhibiting drug (for example, phenelzine), sever symptoms of hypertensive crisis & even death may occur.

Tyramine-containing foods are ordinarily metabolized to a nontoxic substance by monoamine oxidase, which is located within the cells lining the GI tract. Therefore, only a small amount of tyramine is absorbed.

When monoamine oxidase is inhibited, tyramine is not metabolized but absorbed into the blood where it causes toxic pressor activity.

Environmental factors:

- Temperature, &
- Occupation.

Temperature:

- The response of a biologic system to a toxic agent generally decreased as environmental temperature is lowered, but the duration of overall response may be prolonged.

- This is related to a decreased rate of absorption & a lowered rate of metabolic degradation & excretion in colder environments.

Occupation:

- Persons working in industries where organic compounds, such as chlorinated hydrocarbon pesticides or volatile substances, are used may have an enhanced ability to metabolize drugs & chemicals.

- The reason for this is that the chemical's presence in the environment may have caused the induction of liver microsomal enzyme activity.

- The expected reaction to a toxic agent that is normally detoxified by the liver microsomal enzyme system would be reduced. Of course, the reaction would be greater than normal for those substances metabolized to more toxic forms.


Thank
you