

Genetic and Developmental Toxicology

Section 1 - Overview

Michael M. Lipsky, PhD., Professor

Department of Pathology

University of Maryland School of Medicine

MSTF 7-65, 706-7276; mlipsky @umaryland.edu

Learning Objectives:

- 1. To understand the basic concepts and terminology relevant to developmental toxicology;**
- 2. To understand the basic concept of genetic toxicity; and**
- 3 To know the critical periods of susceptibility to developmental toxicants.**

I. General Background - Genetic toxicology

A. Mutagenicity - The ability of chemicals to cause changes in the genetic material in the nucleus of cells (DNA) in ways that allow the changes to be transmitted during cell division

1. the changes must be heritable by daughter cells
2. the change should be irreversible once “fixed” by cell replication. (In this context, “fixed” does not mean repaired but rather the mutation is stabilized in the genome such that it is no longer recognized by the host cell as an alteration to the normal DNA sequence.)
3. Germinal mutations damage DNA in sperm or ova and have the potential to be passed to future generations
4. Somatic mutations - not passed on to future generations passed only to additional cells in the same tissue. These can occur in most cells in the body that can replicate.

B. Gene Mutations - small DNA sequence changes confined to a single gene.

1. Base substitutions
 - Same base (ex. Purine substitution for purine) = transition
 - Different bases(ex. pyrimidine substitution for purine) = transversion
2. Small additions
3. Small deletions
4. Frameshift mutations - addition or deletion of one or a few base pairs in protein coding regions. Not in multiples of 3 bases.
5. Point mutation – mutation occurring by virtue of a change in only 1 base.

II Developmental Toxicology - The study of adverse effects on the developing organism any time during the life span of the organism. It may result from exposure to chemical or physical agents before conception, during prenatal development or postnatally until the time of puberty. This includes pharmacokinetics, mechanisms, pathogenesis and outcomes following exposure to agents leading to abnormal development. Possible outcomes include:

1. structural malformations
2. growth retardation
3. functional impairment
4. death

Teratology - study of defects induced during development between conception and birth
(Structural birth defects)

A. Principals of Developmental Toxicology

- There are critical periods of sensitivity based upon the developmental stage of the conceptus.

1. Immediately after **fertilization** (1 to 6 hr)

2. **Preimplantation** - after an increase in cell number, cleavage and cavitation to form the blastocyst (about 1,000 cells). Only a few of the cells in this mass give rise to the embryo. These cells are in a region called the inner cell mass. Most of the cells go to develop the placenta and supporting tissues.

3. **Implantation to gastrulation** (process of forming the 3 germ cell layers, ectoderm, endoderm and mesoderm).

a. Cells migrate through the primitive streak as a prelude to organogenesis

b. Very susceptible to teratogens at this stage

c. malformations of eyes, brain, face are common and are indicative of damage to anterior neural plate.

4. **Organogenesis**. Within organogenesis there are periods of peak susceptibility for each forming structure. This period of heightened susceptibility is from the 3rd to the 8th week of gestation in humans.

a. organogenesis requires rapid cell proliferation, cell migration, cell to cell interactions and morphogenetic tissue remodeling.

b. Different chemicals with different mechanisms of action may act at different times thereby affecting different organs.

5. **Fetal period** (from day 58 to birth in humans). This is characterized by tissue differentiation, growth and physiological maturation.

a. Exposure during the fetal period most likely to result in effects on growth and functional maturation.

b. Functional anomalies of CNS and reproductive organs, behavioral, mental and motor defects among possible outcomes

c. Major structural alterations can occur during the fetal period but generally result from deformations (disruptions of previously formed normal structures) rather than malformations.

B - Mechanisms and Pathogenesis of Developmental Toxicity

A. Potential mechanisms by which agents may interfere with development

1. Altered energy sources
2. Altered nucleic acid integrity or function
3. Changed membrane characteristics
4. Chromosomal breaks
5. Enzyme inhibition
6. Mitotic interference
7. Lack of precursors
8. Mutation
9. Osmolar imbalance

B. Molecular and cellular mechanisms important in developmental toxicity

1. cell cycle patterns
2. cell lineage
3. cell adhesive interactions
4. cellular migration
5. Chromosomal rearrangements
6. DNA repair
7. Genomic imprinting
8. Growth and differentiation factors
9. Programmed cell death

C. Examples of Developmental Toxins (expanded list in Table 1 of module 2)

1. **Thalidomide** - introduced in 1956 as a sedative/sleep aid and used to ameliorate nausea in pregnancy. It had no apparent toxicity at therapeutic doses in humans (not pregnant). Induced rare limb malformations in newborns in West Germany in the early 1960's.

- a. amelia - absence of limbs
- b. Phocomelia - reduction of long bones of the limbs
- c. congenital heart disease
- d. Other malformations

Of these limb malformations were the most characteristic.

e. never approved for use in US at that time. Chronic animal studies revealed patterns of effects and species sensitivities.

1. No effects observed in hamsters and mice
2. malformations induced in rats, rabbits and non-human primates.

f. Recently FDA approved for limited use in AIDS, diabetic retinopathy and some other disease states. But it is under strict usage guidelines and a special STEP program was developed (System of thalidomide Education and Prescribing safety) for patients and physicians.

2. Diethylstilbestrol - synthetic non-steroidal estrogen used from 1940's to 70's to prevent threatened miscarriage by stimulating estrogen and progesterone in the placenta.

a. Between 1966-1969 7 young women aged 15-22 were diagnosed with clear cell adenocarcinoma of the vagina in Massachusetts.

b. Epidemiological case control study demonstrated an association between this cancer and DES usage in 1st trimester.

c. reproductive anomalies in male offspring also noted.

3. Ethanol - In utero exposure to ethanol causes fetal alcohol syndrome (FAS)

a. FAS comprised of craniofacial dysmorphism, intrauterine and postnatal growth retardation, retarded psychomotor and intellectual development and others.

B. While full blown FAS associated with alcoholic mothers, effects can be with lower levels of alcohol consumption.

4. Tobacco smoke - pre-natal and early postnatal exposure to tobacco smoke may well represent the leading cause of environmentally induced developmental disease and morbidity today.

a. epidemiological studies demonstrate effects of tobacco smoke as: spontaneous abortions, perinatal deaths, increased risk of sudden infant death syndrome, increased learning, behavioral and attention disorders and lower birth weight.

b. nicotine - known neuroteratogen in experimental animals and by itself produces many effects of total tobacco smoke.

5. Cocaine - Local anesthetic with vasoconstrictor properties.

a. Effects on the fetus are complicated and controversial.

b. Usually cocaine exposure not the only exposure

c. Variety of abnormalities observed and include: abruptio placenta, premature labor and delivery, microcephaly, decreased birth weight tremor, poor feeding, SIDS and others.

6. Retinoids

a. Vitamin A has been known to induce malformations for over 40 years.

b. Effects include malformations of the face, limbs, heart, CNS and skeleton

c. In the early 1980's one retinoid was marketed as Accutane and effective treatment for severe cystic acne. Despite clear warnings, an extensive physician and patient education program and restrictive requirements for prescribing to women with child bearing potential reports of infants with malformations began in 1983.

See related article on Accutane:

http://www.fda.gov/fdac/features/2001/201_acne.html