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Teratogenicity: a mechanism based short review on common teratogenic agents

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PEER REVIEW

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Comments

This is a good review in which authors summarized common teratogenic agents, which will help workers who involved in research related to teratology.

Details on Page 430

ABSTRACT

Teratogenicity or reproductive and developmental toxicity has increasingly been recognized as a most important part of overall toxicology. Each compound has its own unique toxicological profile and mechanism of teratogenicity. The present view-point was to explore and review the teratogenic mechanism and common teratogenic effects of teratogenic compounds, biological agents and physical agents. Every year millions of different chemicals are produced and used in the world which contaminate environment and consequently are exposed to human. Many of these chemicals have ability to penetrate into human tissue and developing foetus, negatively impacting the reproductive health of human. Many of the teratogenic effects occur because of biological and physical factors like infection and radiation respectively.

KEYWORDS

Teratogen, Captopril, Phenytoin, Alcohol, Ionising radiations

1. Introduction

Teratogenicity or reproductive toxicity broadly refers to the occurrence of biologically adverse effects on the reproductive system that may result from chemical exposure to several environmental agents which is characterized by alterations to the female or male reproductive organs related to endocrine system, or pregnancy outcomes[1]. Teratogenesis signifies the structural malformations during fetal development, in distinction from other kinds of drug-induced fetal damage such as growth retardation, dysplasia (*e.g.* Iodine-deficiency-related goitre), or the asymmetrical limb reduction[2]. The exposure of teratogenic chemical prior to conception, during prenatal or postnatal development leads to manifestations of developmental toxicity including the death of the developing organism, structural abnormality, altered growth, and functional deficiency[1]. It is estimated that approximately 10%-15% of congenital structural anomalies are the result of the adverse effect of environmental factors on prenatal development[3]. Factors comprise not only chemicals but also micro-organisms including infections, maternal conditions and diseases like diabetes and physical factors like radiations[3,4].

The human teratogen is a chemical drug, metabolic state, physical agent or psychological alteration during development that produce a permanent pathologic or pathopsychologic alteration in the offspring at exposures or circumstances that commonly occur[4]. Birth defects, together with deformation and chromosomal abnormalities, are leading causes of neonatal and postneonatal deaths and

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carry a high social and economic impact[5]. The frequency of malformations is higher in conditions like spontaneous abortions than that in liveborn infants, reflecting the fact that many of the most severe problems are incompatible with survival. Defects in the development of the heart is the most common birth defects and are recognized in about 15% of infants with birth defects. Other common abnormalities include extra fingers and toes (polydactyly), especially on the outer aspect of the hands, webbing between fingers and toes (syndactyly), defects in closure of the developing spine (myelomeningocele), club foot (talipes equinovarus and calcaneovalgus), cleft lip, cleft palate, and incomplete closure of the urethra of the male (hypospadias)[6]. The result of teratogenesis is determined by its site of action and the stage of development of the target organ. These congenital abnormalities are caused by defected genes or exogenous agents. In genetic defects, the scheme indicates the site and stage of development at which the mutant gene is expressed; in nongenetic defects the site and stage refer to exposure to an exogenous teratogen. The four main sites of action of a defective gene or an exogenous teratogen are illustrated in Figure 1. The primary site of action may be on the intracellular compartment (on the chain of interactions between the nucleus and the cytoplasm leading to the specific metabolic products of the cell), abnormalities in the structure and function of the cell surface, extracellular matrix and fetal environment (from abnormalities at the organismal level or in the feto-maternal relation)[6,7].

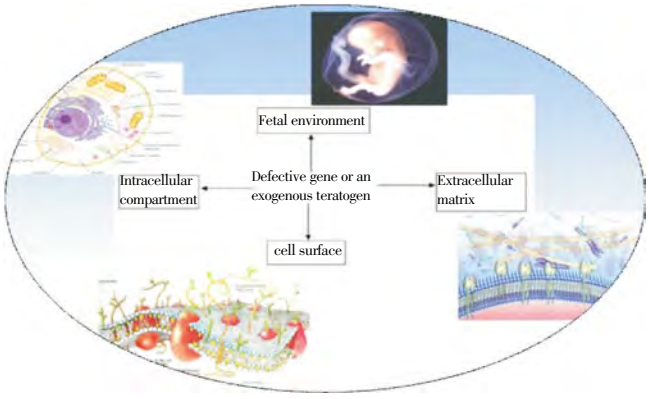

Figure 1. Major sites of action of defective gene or teratogen.

2. General mode of action of teratogen

The timing of the teratogenic insult in relation to fetal development is critical in determining the type and extent of damage. Mammalian fetal development passes through three main phases: blastocyst formation, organogenesis, histogenesis and maturation of function. Many teratogens have ability to inhibit cell division and kill embryo during cell division, which was involved in blastocyst formation. But most of time the embryo survives; its subsequent development does not generally seem to be compromised. Ethanol is one of the causes of teratogen which affects development at this very early stage. Administration of teratogen during the period of organogenesis (Day 17-60) leads to gross malformations. The type of malformation produced by teratogen depends on the time of exposure to organisation of the embryo includes eye and brain, skeleton and limbs, heart and major vessels, palate, and genitourinary system. The cellular mechanisms of teratogens and teratogenic effects are not at all well understood and may produce mutagenic effect, *e.g.* vitamin A derivatives (retinoids), which are involved in morphogenesis and are potent teratogens. Drugs like methotrexate and phenytoin do not react directly with DNA but influence folate metabolism.

The foetus development depends on an adequate supply of nutrients during the final stage of histogenesis and functional maturation, and development is regulated by a variety of hormones. Gross structural malformations do not arise from exposure to mutagens at this stage, but teratogens that interfere with the supply of nutrients or the hormonal milieu may have deleterious effects on its growth and development. A female fetus exposure to androgens can cause masculinisation. Stilbestrol was commonly given to pregnant women with a history of recurrent miscarriage during the 1950s (for unsound reasons) and causes dysplasia of the vagina of the infant and an increased incidence of carcinoma of the vagina in the teens and twenties. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists cause oligohydramnios and renal failure if administered during later stages of pregnancy because of selective inhibition of angiotensin II which plays an important role in the later stages of fetal development and in renal function in the fetus[3-5]. Some of the common human teratogenic agents are listed in Table 1 and their common teratogenic effects are included in Table 2.

Table 1
Common human teratogens.

Category	Examples
Drugs	ACE inhibitors-benazepril, enalapril, captopril
	Acid nonsteroidal anti-inflammatory agent-diclofenac
	Androgen hormones-oestrogen
	Antiepileptics-phenytoin, valproic acid, carbamazepine, trimethadione
	Antineoplastic-folic acid antagonists-methotrexate, amiopterine
	Retinoids-isotretinoin
	Penicillamine
	Thalidomide
	Warfarin
	Xanthine alcoloids-caffeine
	Pesticides-organophosphates
	Herbicides-glyphosate
	Sulfur mustard
Unnecessary chemicals	Alcohol
	Cocaine
Other chemicals	Methyl mercury
Physical agents	Cigarette smoke
	Ionising radiations-high doses at least >5 rad
Biological agents (embryo fetal infections)	Rubella
	Cytomegalovirus
Maternal diseases	Diabetes ID, epilepsy
Phytochemicals	*Veratrum* alkaloid cyclopamine
Miscellaneous agents	Lambda carrageenan

Table 2
Examples of teratogen along with their common teratogenic effect.

Examples	Teratogenic effects	References
Captopril	Intrauterine growth retardation	[8-10]
	Fetal death	
	Neonatal anuria	
	Hypoplastic calvaria	
Diclofenac	Premature closure of the ductus arteriosus	[11-13]
	Decrease of fetal number	
	Skeletal and heart defects	
Oestrogen	Masculinisation of female foetus	[14-16]
	Behaviour changes like rough-and-tumble play	
Phenytoin	Fetal antiepileptic drug syndrome	[17,18]
	Distal phalanges hypoplasia	
	Spina bifida	
	Abnormal nasal bridge and ears	
	Abnormal motor development	
Methotrexate	Skeletal defects	[17,19]
	Low birth weight	
	Disturbed neurulation	
Isotretinoin	Craniofacial abnormalities	[20,21]
	Hydrocephalus	
	Encephalocele	
	Mental retardation	
D-penicillamine	Cutis laxa	[22-24]
	Fetal malformations and death	
Thalidomide	Phocomelia and amelia	[25-27]
	Anotia microtia	
	Hearing loss	
Warfarin	Nasal hypoplasia	[15,17,24,28]
	Spontaneous abortion	
	Distal limb hypoplasia	
	Central nervous system defects and neurological abnormalities	
Caffeine	Expression of several abnormal phenotypes	
Neural tube closure	Craniofacial malformations	[29-31]
	Malformations of the limbs and digits	
Organophosphate	Neural tube defect	[32,33]
	Shortening of pregnancy	
	Decrease in baby birth weight, length and head	
	Anencephaly or spina bifida	
Glyphosate	Shortening of the anterior-posterior axis	[34,35]
	Microcephaly	
	Microphthalmia	
	Cyclopia	
	Craniofacial malformations	
Sulphur mustard	Disruption of nucleic acids and proteins	[36-38]
	Selective cell death of ocular, respiratory and cutaneous tissues	
	Antimitotic, mutagenic, carcinogenic and cytotoxic effects	
Alcohol	Fetal alcohol syndrome	[39,40]
Cocaine	Abruption of placenta	[40-42]
	Disruptive defects on cardio-vascular and autonomic systems	
Methylmercury	Minamata disease	[43,44]
	Cerebral palsy and mental retardation	
	Sensorimotor dysfunction	
Lead acetate	Mental retardation	[45,46]
	Nephrotoxicity	
	Miscarriages and stillbirths	
	Menstrual disturbances	
	Spontaneous abortion	
Cigarette smoking	Intrauterine growth retardation	[47,48]
	Perinatal mortality and morbidity	
	Cardiac defects	
	Chromosomal anomalies	
	Central nervous system defects	
Ionising radiation	Microcephaly	[47-49]
	Skeletal defects	
	Mental retardation	
	Hydrocephaly	
	Microphthalmia	
	Optic atrophy and cataracts	
	Mutations of germ cells	
Cytomegalovirus	Mental retardation	[50,51]
	Oculo-auditory lesions	
	Hepatosplenomegaly, thrombocytopenia	
Rubella	Congenital rubella syndrome	[52-56]
	Cataracts	
	Sensorineural deafness	
	Congenital heart disease	
	Intrauterine growth retardation	
	Retinopathy	
Diabetes	Perinatal mortality	[57-59]
	Congenital defects	
	Dysmorphogenesis	
Epilepsy	Miscarriages	[60,61]
Cyclopamine	Cyclopia	[62,63]
	Holoprosencephaly	
Lambda-carrageenan	Exencephaly	[51,64,65]
	Abnormal beak	
	Anophthalmia	
	Rachischisis	

3. Drugs

3.1. ACE inhibitors: captopril

The ACE inhibitors are competitive inhibitors of kininase II. They affect both the angiotensin/aldosterone and bradykinin/prostaglandin systems. Administration of ACE inhibitors during pregnancy leads to fetal wastage[8]. The fetotoxic effects of ACE inhibitors include fetal hypotension, renal tubular dysplasia, anuria and oligohydramnios, growth restriction, hypocalvaria, and death when used in the second and third trimesters of pregnancy[9].

The administration of these drugs during the second and third trimesters of pregnancy causes high fetal and perinatal mortality. This unfavorable outcome may be related to the reduction in systemic blood pressure and uterine blood flow secondary to the significant vasodilatory effect, possibly caused by a decrease in angiotensin-II production and reduced degradation of bradykinin and prostaglandins mediated by these agents. The reduction in amniotic fluid can also be observed in 30-32 weeks of gestation which might be due to decrease in fetal renal function and urine output[10].

3.2. Acid nonsteroidal anti-inflammatory agents: diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug and commonly used by reproductive age women for the treatment of variety of conditions[11]. Because of its low molecular weight (318.15 Da)[12], diclofenac can readily crosses the human placenta during the first trimester[13]. It is also reported that diclofenac accumulates in fetal tissue[12]. Drugs of this category could increase post-implantation loss, decrease fetal number, induce skeletal and heart defects as well as fetal growth retardation. Pregnant women treated

with high toxic doses of non-selective cyclooxygenase inhibitors show bone developmental variations in fetus[13].

Rats treated with diclofenac on gestation Day 5 showed inhibition of implantation and embryonic development. At high doses (75 μg/mL), it is found to be toxic to rat blastocyst. Drugs of this category like aspirin inhibit synthesis of vasodilator prostaglandin, causing transient vasoconstriction and provoking malformations and cellular death[11].

3.3. Androgen hormones: oestrogen

Exposure of prenatal androgen in animals directly affects masculinization of genitals and brain structures. In male over exposure of androgen leads to more male-typical behaviour like rough-and-tumble play. In humans, androgen levels are far higher in male than female foetuses[14]. Increased level of androgenic hormones during pregnancy causes masculinization of a female foetus. Administration of 17alpha-methyltestosterone, androgenic hormones, produces masculinization and pseudohermaphroditism in pregnant mother.

The androgenic progestin administered to the mother is converted to an oestrogen that does not protect the foetus from the masculinization effect and causes cornification of the vagina[15]. Testicular testosterone produced during a critical perinatal period is thought to masculinize and defeminize the male brain from the inherent feminization program and induce male-typical behaviours in the adult. These actions of testosterone appear to be exerted not through its androgenic activity, but rather through its conversion by brain aromatase into oestrogen, with the consequent activation of oestrogen receptor mediated signaling[16].

3.4. Antiepileptics: phenytoin

Phenytoin is one of the most commonly used antiepileptic medications. It stabilizes voltage-gated sodium channels thereby suppressing abnormal brain activity. Phenytoin is frequently used in trigeminal neuralgia and cardiac antiarrhythmic related conditions[17]. The developing stages of central nervous system (CNS) in the neo natal period have been found to be more vulnerable to the neurotoxic effects of phenytoin because of its higher brain concentration[18].

Exposure during pregnancy has been associated with a constellation of abnormalities sometimes called the fetal hydantoin syndrome that includes abnormalities like short nose, low or broad nasal bridge, epicanthic folds, hypertelorism, microcephaly, abnormal ears, wide mouth, oral clefts, hypoplasia of distal phalanges, short/webbed neck, low hairline, abnormal mental development and abnormal motor development. The prevalence of major and minor malformations was found among the offspring of women taking phenytoin during pregnancy. Polytherapy with anti-epileptic drugs is associated with higher neurotoxic fetal adverse effects than monotherapy[17].

3.5. Antineoplastic: methotrexate

Methotrexate is a synthetic analogue of dihydrofolate and acts as competitive inhibitors of dihydro folate reductase (DHFR) enzyme[17]. Inhibition of DHFR blocks the conversion of DHFR to tetrahydrofolate, which is essential cofactor in the biosynthesis of purines, thymidylate, and some amino acids. The depletion of pool of tetrahydrofolate methotrexate disrupts DNA synthesis and causes rapidly dividing cells to arrest and die. Methotrexate causes disturbance in folate metabolism and may have a teratogenic effect through inhibition of the folate methylation cycle[19]. More likely, intracellular accumulation of homocysteine leads to increased levels of S-adenosylhomocysteine, which is a competitive inhibitor of many methyltransferases, through which gene expression, protein function and the lipid and neurotransmitter metabolisms might be dysregulated. This decreased remethylation of homocysteine to methionine leads to decreased levels of S-adenosylmethionine, which is the most important methyl group donor in the methylation cycle. As a result, neurulation is disturbed by inadequate gene and amino acid methylation. Methylation steps also play an important role in the metabolism of lipids and neurotransmitters and in detoxification of exogenous substances. This stresses the crucial role of the folate metabolism[17].

These effects of methotrexate contribute to potent teratogenicity in humans as well as in animal models[19]. Birth defects in children born to women who have been treated with methotrexate include skeletal defects, low birth weight, and a wide range of developmental abnormalities. The teratogenicity of folate antagonists in humans was first suggested by reports of women who were given aminopterin in the first trimester of pregnancy to induce abortion. Anti-epileptic drugs like carbamazepine and valproic acid increases the risk of folate-sensitive birth defects such as neural tube defects, orofacial clefts and limb defects[17].

3.6. Retinoids: isotretinoin

The isotretinoin (13-cisretinoic acid), a synthetic retinoid, is the drug of choice in the management of severe treatment-resistant acne and is widely used for a range of dermatological conditions. The severe teratogenic effect contains serious craniofacial, cardiovascular, thymic and central nervous system malformations. It has a wide spectrum of side effects, including reproductive, cutaneous,

ocular, neurological, musculoskeletal, and hepatic side effects. The pregnant women exposed to isotretinoin during the first trimester of pregnancy are at high risk level of malformations[20]. It has ability to inhibit the differentiation of sebaceous glands, corrects the keratinisation defect in the follicle and has also some anti-inflammatory activity. However, along with its wide usage, there are growing incidences of its side-effects, and the most important side effect is the teratogenicity[21].

A thoraco-omphalopagus conjoined twin is the most common malformation associated with isotretinoin. It also produces craniofacial abnormalities including ear defects, dysmorphism, cleft palate, depressed nasal bridge and hypertelorism. CNS abnormalities comprise hydrocephalus, microcephaly, facial nerve palsy, and cortical and cerebellar defects. The abnormalities of cardiovascular system consist of tetralogy of fallot, transposition of the great vessels, septal defects and aortic arch hypoplasia. Thymic abnormalities include ectopic, hypoplasia, and aplasia. The drug also produces spina bifida and limb reduction[21].

3.7. Penicillamine

D-penicillamine (DPA) (dimethylcysteine) is a sulfhydryl-containing amino acid and has ability to chelate metals, particularly copper, and increase their rate of excretion in the urine. As dose increased, it decreases concentration of tissue copper level. In many studies it was observed that pregnant women treated with DPA showed fetal malformations. The correlation between low copper levels and a high frequency of fetal malformations and death suggested that copper could be a mediating factor in the expression of fetal abnormalities[22].

DPA has ability to cross placental barrier which could be the reason behind its teratogenic potential. Pregnant women treated with DPA showed severe connective tissue defects in infants. It is a drug of choice in diseases like cystinuria, rheumatoid arthritis and Wilson's disease, and pregnant patients with these diseases are prone to such severe teratogenic effects[23]. The copper dependent enzyme lysyl oxidase is required for the cross-linkage of elastic and collagen fibers in the dermis. The indirect inhibition of the enzyme activity by removal of copper from the tissues by penicillamine causes abnormal elastic fiber accumulation. Also the inhibition of the deamination of the lysine residues by the drug is necessary for elastin and collagen maturation contributing in abnormal elastic fiber accumulation[24].

3.8. Thalidomide

Thalidomide is the worst teratogen known in the history of medicine. Consumption of even very less amount of thalidomide leads to severe limb deformities of the fetus[25]. The limb deformities produced by thalidomide is known as phocomelia and amelia that are characterized by severe shortening or complete absence of legs and or arms, whereas the ear malformations include anotia, microtia and hearing loss[26,27].

Thalidomide has capability to induce reactive oxygen species and oxidative stress which upregulates expression of bone morphogenic proteins through aberrant nuclear Factor-kB activity. This alteration results in blocking fibroblast growth factor (Fgf8/Fgf10), protein kinase B, and signaling proteins pathways known to be important for cell survival and proliferation[27]. Consumption of thalidomide during the first trimester of pregnancy induces dysgenesis of fetal organs. The antiangiogenic effect of thalidomide causes blunting of the growth of long bones in fetal body and leads to cell death and down regulation of growth factors including Fgf8 or Fgf10. The disruption of growth factor signaling pathways is one of the reasons for cell death. This sequence of events produce mesenchymal loss and result in limb deformities[25,27]. It generates free radicals which cause oxidative damage to the embryonic cellular macromolecules and lead to teratogenic effect[25]. In rabbit it was found that thalidomide generated reactive oxygen species, oxidized DNA and accumulated 8-hydroxy-20-deoxyguanosine[27]. Recently, thalidomide-binding protein, cereblon is identified. Thalidomide binds to cereblon and decreases its activity which is supposed to be the primary target of thalidomide teratogenicity[26,27].

3.9. Warfarin

It is a potent naturally occurring coumarin and acts as rodenticide, induces internal hemorrhage in rats and mice. It is also adopted in clinical medicine. Advantages of warfarin are water solubility, oral bioavailability and reversibility by the administration of vitamin[17].

Warfarin is associated with fetal abnormalities[28]. It produces embryotoxicity between 6 and 9 weeks of gestation. Warfarin therapy during pregnancy has been associated with spontaneous abortion, stillbirth, nasal hypoplasia, stippled epiphyses, distal limb hypoplasia and malformations of the CNS, eye, jaw and urinary tract[17]. Microhemorrhages in neuronal tissue due to low stores of vitamin K and low levels of vitamin K dependent procoagulant factors in the fetus are the major factors contributed to CNS defects and neurological abnormalities in children and adults born to women who use warfarin during pregnancy[15,24]. Discontinuation of warfarin from 6 weeks of gestation until the end of first trimester reduces risk of warfarin embryopathy[28].

3.10. Xanthine alkaloids: caffeine

Caffeine is a white crystalline xanthine alkaloid. It is recognized as a stimulant of the CNS because of its ability to enhance alertness. It also produces diuresis, increases heart rate and blood pressure. Caffeine can be easily transfered into the embryo from the external environment and accumulate in the fetal brain that disrupts the normal processes of neuronal development[29]. These characters of caffeine are responsible for its teratogenic effects. In rodents, it produces malformations of the limbs and digits, ectrodactyly, craniofacial malformations (labial and palatal clefts) and delays in ossification of limbs, jaw and sternum. Caffeine also causes thickening of cephalic mesenchymal tissue. In humans, as such caffeine does not cause teratogenicity. However it has ability to potentiate the teratogenic effect of other substances such as tobacco, and alcohol, and acts synergistically with ergotamine and propranolol to induce materno-fetal vasoconstrictions leading to malformations induced by ischemia[30]. In mice, it strongly potentiate the teratogenic action of drugs like mitomycin C and combining administration of caffeine with mitomycin C produced more than 80% of malformed foetuses[31].

3.11. Pesticides: organophosphates

Organophosphorus compounds (OPC) is a wide group of compounds that differs structurally and functionally. Each compound has a unique toxicological profile. Exposure during pregnancy causes malformation in foetus, neural tube defect and shortening of pregnancy[32]. Main teratotoxicity includes decreasing in gestational duration, baby birth weight, body length, and head circumference[33]. Exposure to OPC increases risk of neural tube defects and anencephaly or spina bifida. The exposure of OPC to pregnancy is an important entity because of its effect on two organisms, a mother and a fetus.

OPC selectively inhibits brain cholinesterase but the effect of it is more pronounced in maternal brain as compared to fetal brain maybe due to placental and fetal detoxification of anti-cholinesterase. Brain cholinesterase is inhibited more in young and postnatal animals than that in the adults because of age-related differences to anti-cholinesterase. Congenital malformations are found when mice were treated with formulations of organophosphates[32].

3.12. Herbicides: glyphosate

Glyphosate herbicide formulation and glyphosate alone has potential to cause malformations in the embryos of *Xenopus laevis* and chickens. Previous studies in frogs showed that dilutions of 1/5 000 of the formulation (equivalent to 430 μmol/L of glyphosate) was sufficient to induce malformations like shortening of the anterior-posterior axis, microcephaly, microphthalmia, cyclopia and craniofacial malformations at tadpole stages[34].

Disruption of retinoic acid signaling pathway is the principle mechanism responsible for teratogenic effects of glyphosate-based herbicides (GBH) in *Xenopus* embryos[34,35]. This effect further produce dysregulation of the *shh*, *slug* and *otx2* regulatory genes which are crucial factors of CNS development[34]. GBH also affects embryonic and placental cell, produces mitochondrial damage, necrosis and programmed cell death by activation of caspases with 3/7 left in cell culture. GBH and its principal metabolites, amino-methylphosphonic acid alters cell-cycle checkpoints by interfering with physiological DNA repairing machinery[35]. Skeletal malformations have also been found in mammals treated with glyphosate herbicides[34].

3.13. Sulfur mustard

The bis(2-chlomthyl) sulpha is commonly known as sulphur mustard. It is highly reactive bifunctional compound and produces actions such as antimitotic, mutagenic, carcinogenic, teratogenic and cytotoxic agent. Its powerful vesicant potential has been employed as a chemical warfare agent[36]. Sulfur mustard acts as an alkylating agent that induces disruption of nucleic acids and proteins, impairing cell homeostasis and eventually causing cell death. It selectively reacts with ocular, respiratory and cutaneous tissues, as well as bone marrow and the mucosal cells of the gastrointestinal tract, resulting in several devastating long-term effects on human health[37].

Intravenous administration in male mice results in damage to the testes and inhibition of spermatogenesis. Its reproductive toxicities in human is both lacking and contradictory. It produces significant reduction in testosterone levels during first 5 weeks after exposure whereas luteinizing hormone and follicle-stimulating hormone increase at third and fifth week, respectively[37]. In chick model sulfur mustard produces developmental neurotoxicant by inducing marked deficits in the intermediate part of the hyperstriatum ventrale related imprinting behaviour and concomitant alterations in membrane protein kinase Cγ isoforms[38].

4. Unnecessary chemicals

4.1. Alcohol

The study report related to teratogenic effects of

alcohol was firstly identified and published as fetal alcohol syndrome (FAS) in 1973. FAS refers to pattern of birth defects in children born to women who are heavy drinkers. FAS is characterised by mainly brain, craniofacial and limb abnormalities in children and high risk of mental deficiencies. Teratogenicity of alcohol was dominantly observed in offspring of mothers who have consumed large quantities of alcohol during pregnancy[39]. Several parameters like genetic factors inherited maternally or paternally, can contribute to the fetal susceptibility to alcohol damage. It is considered that alcohol consumption by father may alter his genetic material inherited by the fetus and provide another source of variability and severity in FAS[40].

Alcohol has ability to freely cross placental barrier. The ability of alcohol and one or more of its metabolite like acetaldehyde to cross placenta is the primary cause of FAS. As result of the kinetics of amniotic fluid circulation, and absences or very less of enzymes necessary for drug biotransformation during fetal development, alcohol accumulates in amniotic fluid and acts as reservoir for unchanged alcohol and acetaldehyde. Thus, the embryo fetus is exposed to both compounds long after they have been cleared from the maternal organism[39,40].

4.2. Cocaine

Cocaine is a one of potent psychoactive substance. It has potential to inhibit the post-synaptic re-uptake of catecholamines, dopamine and tryptophan, and blocks sodium ion permeability, resulting in an anesthetic effect. Metabolites like benzoylecgonine and benzoylnorecgonine also have powerful pharmacologic effects and act as neurotoxic. The ability of the drug and its metabolites to cross the placental barrier is responsible to produce sever toxic effect on fetal development. Cocaine affects the maternal cardiovascular and autonomic systems that intern have an indirect effect on the fetal development[40]. The adequate supply of nutrients to fetus and removal of waste products of metabolism depends upon proper functioning of vascular system. During organogenesis, the growth of fetal vascular system as well as morphological changes depends on these requirements. As a result of the dependence on dynamic changes in vessel formation and ablation, fetal growth may be adversely affected by a number of disruptive agents[41].

The potent vasoconstrictive effects of cocaine when exposed during the first trimester may increase the risk of structural abnormalities[41]. The women treated with cocaine showed placental abruption (premature separation of a normally implanted placenta) which is one of significant causes of maternal morbidity and fetal mortality. This effect may be due to maternal hypertension caused by the drug[42]. Administration of cocaine to pregnant ewes causes dose dependent acute decrease in uterine blood flow which causes to decrease in fetal arterial oxygen partial pressure and oxygen content and leads to destruction of fetal tissue and organ malformation. Cocaine exposure increases fetal cardiovascular effects like heart rate, mean arterial pressure as a result of accompanying fetal hypoxaemia and the production of fetal catecholamines[41].

5. Other chemicals

5.1. Methylmercury

Methylmercury is popularly known for its variable toxicity such as neurotoxin, endocrine disruptor and teratogen. Exposure to methylmercury produces changes in behaviour and health in humans and wildlife[43]. Consumption of methylmercury contaminated food such as fish is common reasons for exposure. Prenatal exposures of humans at high concentration result in neurobehavioral effects such as cerebral palsy and severe mental retardation. It is also associated with decreased birth weight and early sensorimotor dysfunction such as delayed onset of walking. Exposure studies on nonhuman primates and rodents showed neurobehavioral changes. It also produces developmental neurotoxic effects in fetus and infant. To avoid these teratogenic effects, pregnant women and women of childbearing age are recommended to avoid exposure of methylmercury[44].

5.2. Lead acetate

Lead is common occupational and public health problem that causes several adverse effects in both men and women. Previous experimental study revealed nephrotoxicity of lead. Exposure to high dose affects the reproductive function in both female and male. Miscarriages and stillbirths frequency increases in female exposed to lead. Serious effects of lead exposure comprise increased prevalence of menstrual disturbances, spontaneous abortion and threatened abortion[45].

Oral administration of lead acetate was reported to arrest growth and maturation of the ovarian follicles in mice[45]. It also produces toxic effects on the sperm in the offspring male mice resulting in abnormal morphology of spermatozoa. This effect of it is disturbances in the phases of spermatogenesis and spermiogenesis as it upset metabolic activity of the sertoli cells. It is also have

ability to pass through the placenta of pregnant mice and reach and accumulate within the tissues of fetus[46].

6. Physical agents

6.1. Cigarette smoking

Cigarette smoking by the mother is one of major reasons of general developmental abnormalities. Reduced growth in fetus is observed. The array of chemicals like nicotine, carbon monoxide and cyanide released during tobacco smoking interfere with the transport of amino acids across the placenta. Several mechanisms have been proposed like placental necrosis, inhibition of placental exchange and activation of metabolic enzyme based toxic reactive metabolites that produce teratogenic effect, but exact mechanism responsible for teratogenic effects in human is unclear[47].

Carbon monoxide produced during smoking crosses placenta and increases carboxyhemoglobin levels in blood which has longer half-life in fetal blood than in maternal blood. Nicotine released during cigarette smoking has vasoconstriction effect that results in uterine vascular constriction and intrauterine growth retardation because of decreased perfusion of fetal tissues. It also increases the risk of perinatal mortality and morbidity[3]. The perinatal mortality is attributed to abruption placentae, placenta previa, spontaneous abortion, prematurity and intrauterine growth retardation, preterm delivery, perinatal mortality, subfertility, abnormal placentation, childhood morbidity and mortality, congenital malformations, gastroschisis, cardiac defects, chromosomal anomalies and central nervous system defects[48].

6.2. Ionizing radiation

The cell death or chromosome injury is the common reasons of embryo injury by ionizing radiation. Exposure of radiations 8-15 weeks after fertilization is the most critical exposure period leading to toxicity. Before implantation exposure to radiation causes teratogenic and growth-retarding effects. The exposure leads to several effects such as human embryos abortion, malformations, intrauterine growth retardation and has early- or late-stage onset genetic disease of which permanent growth retardation is more severe[49]. The CNS is predominantly affected by radiation exposure and leads to CNS abnormalities like early microcephaly, mental retardation and later increases incidence of hematopoietic malignancies and leukaemia[47].

In early 19th century, X-ray radiation was used to induce abortions. A single dose of 360 rads is enough to kill a fetus before the 14th week of gestation. The common teratogenic effects of radiation exposure are defects in the brain and eyes like microcephaly, hydrocephaly, microphthalmia, optic atrophy and cataracts. Skeletal, visceral and genital abnormalities are less frequent. Small doses of radiation may induce mutations of germ cells. Excessive exposure to radiation causes chromosomal fragmentation, and alters DNA structure leading to mutations. It also impairs cell division and produces cell death and malignancy.

Even a small dose of radiation (10 rads) will kill preimplantation embryos.

7. Biological agents (embryo-fetal infections)

7.1. Cytomegalovirus (CMV)

Infection of viruses like congenital CMV is a major public health concern. CMV causes serious neurodevelopmental sequelae, including mental retardation, cerebral palsy and sensorineural hearing loss. The teratogenic effects of CMV is because of its ability to disrupt normal cellular differentiation and morphogenesis pathways, the impact on apoptosis and antiapoptotic mechanisms, the role of neural stem cells, the critical developmental windows of susceptibility, the role of the inflammatory processes in potentiating CNS injury, and the potential pathogenic impact on the endovascular system[50].

Several studies revealed CMV infection inducing birth defects. These effects are either by direct chromosomal injury or by modulation of developmental gene expression. Human fibroblasts study showed that infection of CMV during the synthesis phase of the cell cycle resulted in two specific chromosome 1 breaks at positions 1q42 and 1q21. Mechanisms like apoptosis, "autodestructive pathway" has physiological role in maintaining homeostasis of body and is also considered as a critical defence mechanism to purge pathogens like virus-infected cells from the host[50]. Regulation of apoptosis in the mammalian cell is by two pathways, intrinsic pathway, triggers cellular sensor proteins such as p53 and initiates a cascade of biochemical signals leading to the mitochondrial release of cytochrome-c and an extrinsic pathway which is activated by external signals, primarily involving the immune system, and consequent phosphorylation of receptor death domains, such as those in the tumour necrosis factor receptor family and FAS, by their respective ligand. Further these apoptotic signals induce the activation of the caspase family of proteases. CMVs have evolved mechanisms to delay the intrinsic apoptotic signaling pathway, presumably to allow time for completion of their relatively slow replication cycles. The major transcriptional regulators of viral

replication are IE proteins, IE1 and IE2 and have ability to inhibit the process of apoptosis. On infection with CMV human astrocytes turn over phosphatidylserine molecules to the extracellular surface, an early cellular alteration that marks apoptotic cells for destruction by macrophages. This leads to delaying in subsequent nuclear changes (DNA degradation) in the apoptotic cycle until next viral replication cycle[50]. Although majority of congenital CMV infections are asymptomatic in newborn, some of them show sequelae later in life and they may produces long-time cognitive outcomes[51].

7.2. Rubella

The severity of birth defect produced by rubella in the United States is well known but the pathogenesis of rubella-induced birth defects is still unclear, although it produces a spectrum of defects as distinctive as those produced by any other teratogen[52]. The major teratogenic effects are miscarriage, fetal death, or birth of an infant with congenital rubella syndrome[53]. Infection of rubella in the first 16 weeks of gestation produces birth defects whereas infection in the fifth month or later does not usually cause disability. In certain cases it was observed that infection during 28 weeks causes deafness, during 24 weeks causes peripheral pulmonary artery stenosis and there may be growth retardation associated with third trimester infection. Deafness, eye defects such as cataracts, cardiovascular defects, particularly patent ductus arteriosus, and CNS damage leading to mental retardation are the main defects associated with rubella infection[52].

The transient abnormalities associated with congenital rubella syndrome include intrauterine growth retardation, jaundice, purpura and/or a blueberry muffin rash, swollen lymph glands, low platelet count, abnormalities at the ends of the femur and humerus on X-ray exposure, enlarged liver and spleen (hepatosplenomegaly), meningoencephalitis (infection of brain), pneumonia, myocarditis (inflammation of the heart muscle), anemia, cloudy cornea of the eye whereas permanent abnormalities present at birth or manifest over a lifetime comprise growth retardation, hearing loss (sensorineural hearing loss and deafness), visual loss (cataracts, microphthalmia, retinopathy, corneal opacity, glaucoma, nystagmus, retinal detachment, sub retinal neovascularization, keratoconus, lens absorption, blindness), congenital heart defects [patent ductus arteriosus, peripheral pulmonary stenosis (narrowing), pulmonary valve stenosis (narrowing), ventricular septal defect, atrial septal defect], abnormalities of blood vessels (renal artery stenosis, high blood pressure and arteriosclerosis), genitourinary abnormalities (undescended testicles, inguinal hernia, hypospadius and polycystic ovaries), gastrointestinal problems (gastroesophageal reflux, esophageal stricture, gagging, cyclic vomiting, swallowing difficulties, and cirrhosis of the liver), endocrine abnormalities [hyperthyroidism, hypothyroidism thyroiditis, addison's disease (adrenal insufficiency), excessive hairiness in females (hirsutism), polyglandular autoimmune disease, growth hormone deficiency, diabetes, and precocious (early onset) puberty], CNS abnormalities [microcephaly (small head size), mental retardation (mild, moderate, severe, profound), autism, progressive rubella panencephalitis, cerebral palsy, behaviour problems (self stimulatory, self-abusive, self-injurious, impulsivity, tantrums), intracranial calcifications and seizures] and abnormal teeth[54,55].

Fetal damage produced by rubella is multifactorial, resulting from combination of rubella-virus-induced cellular damage and the effect of the virus on dividing cells. Placental infection of virus causes maternal viraemia, resulting in necrosis of epithelium of chorionic villi and capillary endothelial cells. This further leads to transfer of rubella virus into the fetal circulation as infected endothelial cell emboli, which may result in infection and damage of fetal organs. Because of immature fetal defence mechanisms rubella infection produces rubella embryopathy (cellular necrosis) in early gestation period[56].

8. Maternal diseases

8.1. Diabetes

Offspring of insulin dependent diabetic mothers are highly prone to congenital malformations and represent the major cause of perinatal mortality in these infants. The mechanisms responsible for these effects are poorly understood. Metabolic alteration in diabetes increases synthesis of basement membrane components that play a major role in morphogenesis. Previous rat study showed that maternal diabetes selectively alters gene expression in the developing rat embryo and the changes involve molecules (extracellular matrix components) that are critically important in morphogenesis[57]. Also changes were observed in mRNA and cognate proteins. Altered activity and protein distribution of several protein kinase C isoforms were observed in embryos of diabetic rat[58]. Presence of hypoglycaemic state during the early phase of organogenesis produces teratogenic effects in the rats. Normal development of rats during this phase depends on uninterrupted glycolysis and its interruption leads to dysmorphogenesis[59].

8.2. Epilepsy

Mothers suffering from epilepsy have two to three fold

higher risks of congenital malformations than the general population and the major reason behind these malformations is antiepileptic therapy. Although antiepileptic therapy diminishes seizure frequency, the malformation rate increases[60]. Seizures during pregnancy can cause harm to the unborn baby. Chances of miscarriages increase in pregnant epileptic mother suffering from grand mal seizures or generalized tonic-clonic seizures.

Polytherapy (multiple antiepileptic drugs at the same time) and increased dose are mainly associated increased incidences of congenital malformations. It causes both major and minor congenital abnormalities. Major anomalies include neural tube defects (such as spina bifida), cardiac defects, microcephaly, cleft lip/cleft palate, urogenital anomaly and developmental delay whereas minor malformations include craniofacial anomalies, digital anomaly and hypoplasia. Mechanisms responsible for these anomalies are unknown and likely multi-factorial[61].

9. Phytochemicals: *Veratrum alkaloid* (cyclopamine)

In Indian medicinal system, herbal drugs have been used since ancient times as medicines for the treatment of a wide range of diseases. Certain plants like gossypol, *Tripterygium wilfordii* and *Ecballium elaterium* have contraceptive efficacy. These effects are because of presence of specific phytochemicals. The steroidal alkaloid cyclopamine has ability to produce cyclopia and holoprosencephaly when administered to gastrulation stage amniote embryos. Holoprosencephaly is a malformation sequence developed from impaired midline cleavage of the embryonic forebrain, is expressed as a spectrum of craniofacial anomalies of which cyclopia is the most severe[62]. Cyclopamine-induced malformations in chick embryos are associated with interruption of Sonic hedgehog-mediated dorsoventral patterning of the neural tube and somites[63].

10. Miscellaneous agents: lambda-carrageenan

Lambda-carrageenan is a food additive. Exposure of lambda-carrageenan to the yolk sac of fertile chicken eggs leads to teratogenic and lethal effects on chick embryo development. Malformations were mainly localized in the cephalic end (exencephaly, abnormal beak, anophthalmia)[51]. Carrageenan-induced malformations generally associated with increased cell proliferation and defective closure of the neural tube[64].

The mechanism that leads to teratogenic effect in the chick embryo is still unclear. Degradation of carrageenan releases galactose which has teratogenic properties and is considered as one of reasons for carrageenan teratogenicity. Also polyglycoside released during carrageenan metabolism may interfere with normal cell movement and intercellular attachment by blocking cell surface components[65]. In the process of neural tube formation the first contact between the neural folds takes place at the glycocalyx of the approaching zones which presumably include the luminal surface of neural crest cell precursors. Study on carrageenan exposed embryos showed damaged glycocalyx of the neural surface at the level of rachischisis and leads to failure of closing of the neural tube that might be responsible anomalies[64].

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Teratogenicity or reproductive and developmental toxicity has increasingly been recognized as a most important part of overall toxicology. Each compound has its own unique toxicological profile and mechanism of teratogenicity. The present view-point was to explore and review the teratogenic mechanism and common teratogenic effects of teratogenic compounds, biological agents and physical agents.

Research frontiers

It might be helpful to improve knowledge of teratogens. It focuses on the molecular targets involved in abnormal response to teratogens.

Related reports

The concepts regarding teratogenic compounds and teratogenic effects have been neatly described. A lot of related references have been cited.

Innovations & breakthroughs

The manuscript 'teratogenicity': a mechanism based short review on common teratogenic agents involves almost all the

data related to common teratogens, mechanism and their teratogenic effects.

Applications

The present manuscript has good applicability to find targets for the management of teratogenic effects of teratogens. It will help the people who involved in research related to teratology. All the mechanism explained in very simple language.

Peer review

This is a good review in which authors summarized common teratogenic agents, which will help workers who involved in research related to teratology.

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