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Review Article

Endocrinal toxicity of industrial solvents – A mini review

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Endocrine system can be affected by various organic compounds. The review describes the effects of major industrial solvents on adrenal, thyroid and parathyroid glands in man and experimental animals. Further, their toxicity in pancreas, pituitary, testis and ovary has also been discussed. An attempt has been made to offer a historical and general information on solvent toxicity in endocrine glands. Possible mechanisms, in brief, have also been discussed. Endocrine toxicity caused by industrial solvents deserves more attention than hitherto paid. An understanding of hormonal disorders caused by industrial solvents will be important from occupational health point of view.

Keywords: Adrenal, Endocrinal disruption, Gonads, Industrial solvents, Thyroid

Outline

Over the last two decades, there has been increasing scientific concern and public debate regarding the adverse effects of chemical pollutants present in the environment that can interfere with the normal functioning of the endocrine system in wildlife and in humans (the so-called endocrine-disrupting chemicals, EDCs). These concerns have been fuelled primarily by reports of disrupted reproductive function and development in certain wild-mammals, birds, fish, amphibians, mollusks and by the increased incidence of certain diseases of the endocrine system in humans. Some of the adverse effects observed in several species are strongly associated with exposure to chemicals that mimic or interfere with hormone function, particularly estrogen function, but in many cases, the causal link between exposure to EDCs and endocrine disruption is unclear. Because of the diverse effects of EDCs on the thyroid, retinoid, androgen, estrogen, and corticosteroid systems of a wide range of animals, it is imperative to address the extent of the risk posed by EDCs to wildlife and man. The ecological relevance of endocrine disruption is, however, difficult to quantify, as there is limited understanding of how physiological changes affect the individual animal and how individual responses affect population and community. Further, a major challenge faced by environmental biologists is the need to place endocrine disruption into context with other environmental pressures faced by populations, viz. global warming and climate change.

Introduction

An endocrine gland is composed of a prominent mass or parenchyma of secretary cells as well as connective tissue, blood vessels and nerves. Endocrine glands secrete their products (hormones) directly into the bloodstream. Hormones were originally considered to be synthesized within specific endocrine organs and then secreted into the bloodstream to act on specific target tissues distance away to evoke a specific metabolic/physiological response[1]. Hormones activate very specific cells or target tissues. The identification of hormones in single cell organisms confirms the specificity of hormones to particular biochemical pathways within a cell. This specificity of hormones is achieved by finally tuned regulation of specific receptors for each hormone. Receptors response is highly specific. Receptors are found in membranes and within the cytoplasm of cells. There are two principal pathways for receptor activation. Firstly, there are receptors on the plasma membrane for protein and peptide hormones. Secondly, there are cytoplasmic or nuclear receptors for lipophilic moieties such as thyroid and steroid hormones. Many receptors for endocrine target organs

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are ligand-dependent transcriptional regulators that belong to a super family of proteins that include oestrogens, androgens, retinoic acid, thyroid hormones and vitamin D. These hormones, having molecular weights between 300 and 400 Da, can permeate the plasma membrane. Once they enter the cell, these hormones can bind to specific protein both in the cytoplasm or the nucleus[2]. The mechanism of action of hormones has been categorized into two groups. The hormones in group 1 are lipophilic. These hormones bind to intracellular receptors in the cytoplasm or the nucleus and cause confirmational changes. The hormone-receptor complex then binds to a specific region on DNA called the hormone response element (HRE). This interaction with the help of various accessory factors and co-regulators, results in the activation or repression of a restricted number of genes. The hormone response elements and associated factor elements are called hormone response units[3] (Fig. 1).

Group II hormones are water soluble and initiate a response by binding to a receptor located in the plasma membrane. Cyclic AMP (3', 5'-adenylic acid) a ubiquitous nucleotide derived from adenosine triphosphate (ATP) through the action of the enzyme adenylate cyclase plays a vital role in the action of several hormones. The intracellular level of cAMP is increased by hormones of this group and they do so through unique receptors converging on a single class of adenylate cyclase molecules.

Endocrinal disruptors

There is increasing evidence that some industrial chemicals including solvents may interfere with complex and carefully regulated hormonal messenger system of our bodies. The public, scientific and regulatory concern regarding the potential adverse health impacts of exposure to endocrine-disrupting chemicals have been reviewed by several reports published in early decades[4-16]. However, all these reports were limited to the single system or the particular endocrinal disrupting xenobiotic. During 31 March to 1 April 2004, a workshop was conducted in Mallorca, Spain on multi-organic risk assessment of EDCs. The objective of workshop was to develop risk assessment methods considering mixed exposures and low dose effects[17].

The possible disruption of endocrine systems by environmental chemicals and the effects on human health have become major topics of discussion and

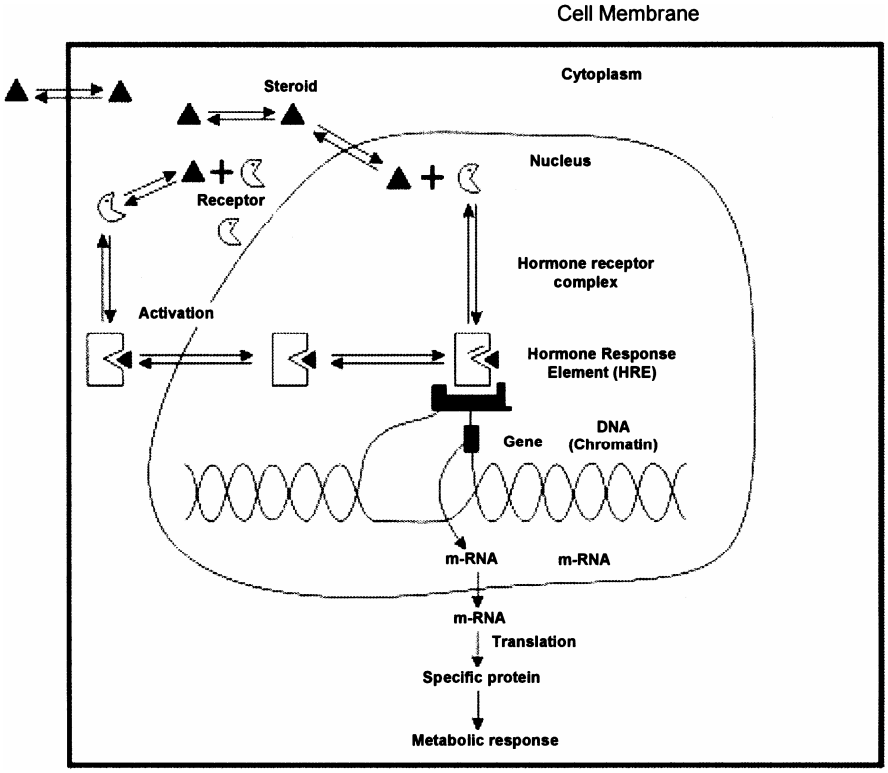

Fig. 1—Mechanism of action of lipophilic hormones (ref. 3)

research in past few years[18]. The issue of "environmental endocrine disruptors" is now a key topic on the agenda of groups in government, industry and toxicologists. In order to establish a common basis for discussion and to enable the identification of active substances, it is important to develop a precise definition of an endocrine disruptor[19]. There have been several attempts to describe the phrase but there is as yet no universally accepted definition of endocrine disruptor. Kavlock[20] defined an endocrinal disruptor as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental process"[21]. However, another definition recently accepted during an European workshop on endocrine disruptors states:

"An endocrine disruptor is an exogenous substance or mixture that causes adverse health effects in an intact organism or its progeny, subsequent to change in endocrine function"[22].

A large number of man-made chemicals that have been released into the environment as well as a few natural ones, have the potential to disrupt the endocrine system of animals and humans. There are persistent, bioaccumulative organohalogen compounds that include some fungicides, herbicides, insecticides and industrial chemicals and other synthetic products. Wildlife including birds and fish, zebrafish, shellfish and mammals are also affected by these compounds[7,23-27]. Due to their similarity during early embryonic development, researchers used the data acquired on these species to make predictions about endocrine disrupting effects of chemicals on humans.

Toxicity of organic solvents

Organic solvents refer to a group of volatile compounds or mixtures with low molecular weight that are relatively stable chemically and that exist in the liquid state at temperatures of approximately 0° – 250°C (32° – 482°F). Common organic solvents are classified as aliphatic hydrocarbons, cyclic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, ketones, amines, esters, alcohols, aldehydes and ethers. Many common solvents often exist as mixtures or blends of chemical compounds[28]. Organic solvents are used for extracting, dissolving or suspending materials such as fats, waxes and resins that are not soluble in water. The removal of the solvent from a solution permits the recovery of the solute intact with its original properties[29]. Solvents are used in paints, adhesives, cosmetics, glues, polymers, plastics, textiles, printing inks, agricultural products and pharmaceuticals[28]. Approximately 9.8 million workers are potentially exposed to organic solvents[30]. They share properties such as lipophilicity and volatility. Some of solvents are hydrophilic or less volatile. In general, inhalation and skin absorption represent significant routes of exposure to organic solvents. The uptake of vapour by inhalation is a simple physical process, the molecules diffuse from the alveolar space into the blood, where they dissolve. The molecules partition between two media—between air and blood during the absorptive phase and between blood and other tissues during the distribution phase. The more soluble a vapour is in the blood, the more of it will be absorbed into the blood during each respiratory cycle. The amount of vapour taken up by various tissues depends on the affinity of the organic solvent for each tissue. Thus the rate of the absorption of organic solvents in the lungs and distribution of various tissues including endocrine glands are variable and depend on the blood-gas and fat-blood partition coefficients[31]. Major organic solvents proved or suspected as endocrinal disruptors are summarized in Table 1.

Specific endocrine system as targets of organic solvents

Endocrine system can be affected by various organic compounds. Some endocrine organs appear to be more sensitive to toxic agents including organic solvents and often lead to multiple disruptions in the hormonal balance of the organism.

Generally chemically induced changes that affect the endocrinal organs seldom manifest after a single exposure to a toxic agent. Rather, solvents that have the potential to exert deleterious effects upon the endocrine system ordinarily require longer durations of exposure and repeated administrations. Depending upon the particular chemical, the sites of action may differ in their sensitivity to toxic agents. A physiological hierarchy of control regulates and counter-regulates the homeostasis of the endocrine system through a series of feed back mechanisms. Feed-back is the modulation of output by an end-product or product (hormone or metabolite). A negative feed back mechanism inhibits an endocrine

Table 1—List of some organic solvents as endocrinal disruptors

1.	Benzene	22.	n-hexane
2.	Benzyl chloride	23.	Thiols
3.	Ethyl acetate	24.	1,1,1-trichloroethane
4.	Carbon disulfide	25.	1,1,2-trichloroethane
5.	Carbon tetra-chloride	26.	Trichloroethylene
6.	Chloroethane	27.	Pentachloroethane
7.	Chloroform	28.	Styrene
8.	Chloroprene	29.	1,1,1,2-tetrachloroethane
9.	Cresol	30.	1,1,2,2-tetrachloroethane
10.	Di-2-ethyl hexyl phthalate	31.	Vinyl acetate
11.	Dioxin	32.	Xylene
12.	Epichlorohydrin (Suspected)	33.	Phenols
13.	Ethylene dibro-mide	34.	Ethyl benzene
14.	Ethylene dichlo-ride	35.	1,4-bio[2-(3,5-dichloropyridyloxy)]benzene
15.	Furfuryl alcohol	36.	Polychlorinated biphenyls (PCBs)
16.	Glycol ethers	37.	m-dinitrobenzene
17.	Isopropyl alco-hol	38.	Bromo trichloroethane
18.	Ketones	39.	Carbon tetra bromide
19.	Methyl alcohol	40.	Benzyl bromide
20.	Nitriles	41.	Benzene hexachloride
21.	Toluene	42.	Tobacco smoke (containing many organic solvents)

pathway whereas positive feed back loop enhances an endocrine response. Feed back mechanisms can further be modulated by other endocrine systems that are either pulsatile, cyclical or stimulated through other mechanisms[2].

The concept of the endocrine system is that endocrine cells release a hormone that is transported to a receptor site in a target tissue where the hormone binds and exerts its biological effects. Perturbation of a target organ by a chemical can be mediated through central nervous system by interfering with trophic hormone secretion and also occur by a chemical acting directly upon the particular target organ. Further, hepatic microsomal enzyme system responsible for endogenous steroid metabolism can be affected by organic solvents[32,33].

Adrenal toxicity

Adrenal cortex is a multifunctional steroidogenic organ. Adrenal glands have many features which render them susceptible to toxicological insult including high membrane content of unsaturated fatty acid, high rate of blood flow, free radical generation during steroid biosynthesis, potential for bioactivation of xenobiotics by cytochrome P_{450} enzymes, mechanism for uptake and storage of lipoprotein. The adrenal cortex secretes a range of steroid hormones, which are produced from cholesterol by reactions mainly catalyzed by cytochrome P_{450}[34]. The enzymes of steroid biosynthesis are targets for various toxicants including organic solvents[35,36]. Adrenal insufficiency as a result of organic solvent exposure causes severe changes in electrolytes and carbohydrate metabolism, leading to circulatory collapse, hypoglycaemia, coma and sometime death. Trichloroethylene toxicity of adrenal glands has been described by Mazza and Brancaccio[37]. The cortex and medulla integrate many biochemical changes in the internal and external environment. The adrenal cortex is vulnerable to chemical lesions[38]. Various solvents cause severe damage to adrenal cortex. Carbon tetrachloride alters the adrenal gland secretion and causes adreno-cortical necrosis[39]. Acrylonitrile produces adrenal necrosis in animals[40]. Chemically induced dysfunction of adrenal gland has been reported[41]. Toluene elevates corticosterone on inhalation[42]. The effects of several drugs and chemicals on the structure of adrenal gland were described by Ribelin[43]. Benzene and toluene exposure stimulated hypothalamic pituitary adrenocortical activity. Elevated corticosterone has also been reported to inhibit IL-2 production and impair immunocompetence[44]. Transplacental toxicity of 3-methylsulphonyl-DDE in the developing adrenal cortex in mice was reported by Jonsson[45]. Cytochrome P_{450} catalyzed the binding of 3-methyl-sulfonyl-DDE and o,p-DDD in human adrenal zona fasciculata and zona reticularis[46]. Toluene inhalation induces the adrenocortical hypertrophy in rat[47]. An adrenal dependent leucopenia after short term exposure to air borne irritants viz. acetic acid, benzyl chloride, 1,1-dichlorobenzene, ethyl acetate, ethyl acrylate, formaldehyde, isophorane, mesityloxide, phenol, styrene, toluene and vinyl toluene was reported by Brondeau[48]. Adrenal cortex and medulla function may be altered by benzene, dioxane, tetrachloroethylene, PCB and TCDD also[49]. Recently, the effects of endocrine disrupting chemicals on adrenal function have been studied[50].

Thyroid toxicity

The function of the thyroid is to elaborate, store and release thyroid hormones into the bloodstream. Available literatures on the toxic effects of various

organic solvents shows that poly halogenated biphenyls affect thyroid gland metabolism in a number of animals[51]. Hyperthyroidism is known to augment hepatic sensitivity to chloroform[52]. The effect of carbon tetrachloride is aggravated by the administration of thyroxine[53]. Specific chemicals appear to have a direct effect on the thyroid gland resulting in genetic damage that leads to cell transformation and tumor formation. Examples of thyroid initiaters include 2-acetylamino fluorine, dichlorobenzidine, N-methyl-N-nitrosourea, methyl cholanthrene and polycyclic hydrocarbons. Multiple sites of hypothalamic pituitary thyroid triad exhibited by chemicals that develop an increased incidence of hyperplastic and/or neoplastic lesions are shown in Fig. 2.

Study on the inhalation toxicity of methanol, toluene and mixtures of both the chemicals revealed that thyroid gland in females appeared to be a target organ, although the changes were confined to a mild and occasionally moderate reduction in follicular size[55]. Thyroid gland follicular cell hyperplasia was also observed after the exposure to ethyl benzene[56].

1,4-bio[2-(3,5-dichloropyridyloxy)] benzene promotes the thyroid carcinogenesis in rat[57]. Mixtures of 3,3',4,4',5-pentachlorobiphenyl and 2,2'4,4',5,5'-hexachlorobiphenyl in female Harlen Sprague-Dawley rats alters the serum thyroid hormone levels[58]. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) acts as a potent and persistent thyroxine agonist[59,60]. Schmutzler[61] reported the effect of endocrine active compounds on thyroid hormone levels in serum and its action in liver, heart and kidney. Thyroid toxicity due to subchronic exposure to a complex mixture of sixteen organo chlorines has also been documented[62].

Parathyroid toxicity

Parathyroid glands are composed of a single cell type concerned with the biosynthesis of parathormone. Relatively few solvents are known to cause parathyroid toxicity. Di-propylene glycol causes the secondary lesions in the parathyroid of male rats[63]. Our studies have shown that parathyroidectomy modulates liver injury caused by CCl_4 in rat[64-68]. Solvent toxicity in parathyroid glands, however, remains unknown.

Pancreas toxicity

The endocrine pancreas by secreting the polypeptide hormones i.e. insulin and glucagon controls blood

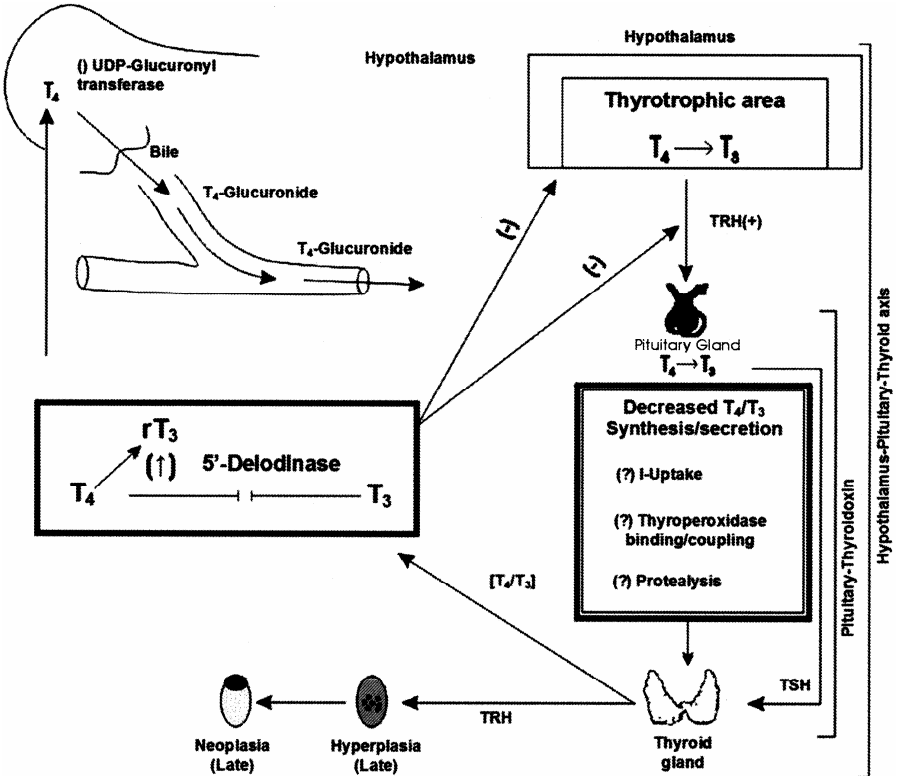

Fig. 2—Multiple sites of hypothalamic-pituitary-thyroid triad exhibited by chemicals that develop an increased incidence of hyperplastic and/or neoplastic lesions (ref. 54).

glucose levels. These hormones have opposite actions; while insulin promoting glucose uptake and utilization by tissues, the glucagon facilitating glycogenolysis and gluconeogenesis. Abnormal regulation of blood glucose leading to hyperglycemia is a characteristic of diabetes, a multifaceted disease characterized by deficiencies in the function of the endocrine pancreas particularly the insulin secreting β-cells[69]. Heavy alcohol consumption is a potential risk factor for induction of pancreatitis[70,71]. In an earlier study, functional state of pancreas in workers engaged in industries using benzene was described[72]. Increased bile duct pancreatic fluid flow in benzene and halogenated benzene treated rats was also studied[73]. The occupational exposure to polycyclic aromatic hydrocarbons and k-ras activation in human exocrine pancreatic cancer was studied[74]. A study on cancer incidence of pancreas among Finnish workers exposed to aromatic hydrocarbons (styrene, toluene, xylene) has been made[75]. The effects of benzoic acid and its analogue on insulin and glucagon secretion were studied in sheep[76]. Gasoline containing benzene, toluene 1,3-butadiene, ethyl benzene, xylene, trimethyl pentane, methyltertbutylethane (MTBE) produced the cancer of pancreas in workers engaged in oil refinary and petrochemical industry[77,78]. A fatal case of oral ingestion of toluene and its distribution in tissues including pancreas was also studied[79]. *In vitro* effects of polyphenol on activity expression and secretion of pancreatic bile salt dependent lipase were described by Sbarra and coworkers[80]. A very interesting study, described the chronic pancreatitis in cigarette smoking patients[81]. The study revealed expression of p-53 protein in chronic pancreatitic patients. 2,4-dimethoxy-2-methylnaphthalene (DMN) potentiated the apoptosis of pancreatic acinar cells after induction of menadione[82]. Endocrine pancreas deserves special attention since exposure to many xenobiotics can contribute in the etiology of diabetes mellitus.

Pituitary gland toxicity

Pituitary functions can be altered by many endogenous and exogenous agents[83]. Generally chemical induced changes that affect pituitary target organ relationships seldom manifest after a single exposure of a toxic agent. Polychlorinated biphenyls (PCBs) are persistent food contaminants that have adverse effects on the pituitary gland[84]. Another study described the effect of chloroform narcosis and other narcosis on the activity of basic carboxy-peptidases in the hypothalamic- pituitary- adrenal axis in rats[85].

However, bromodichloromethane decreased the incidence of pituitary gland tumors in female rats and in female mice[86]. Ethanol induces oxidative damage in the pituitary gland[87]. Chronic inhalation of hexane by female F-344 rats and B6C3F1 mice produced pituitary adenomas[88]. Role of pituitary hormones in the regulation of hepatic cytochrome P_{450}2E1 in rats and mice was also studied[89]. The fetal pituitary gonadotropin was reported to be an initial target in the impairment of cholesterol transportation and steroidogenesis in rats[90]. Cell death in ALT-20 pituitary cells was induced by 2,3,7,8-TCDD[91]. Induction of 7-ethoxyresorufin-o-deethylase activity by chlorinated hydrocarbons and polycyclic aromatic hydrocarbons in cell lines was reported from the rainbow trout pituitary[92]. Effects of various occupational agents' viz. benzene, dioxane, styrene, tetrachloroethylene and toluene on the endocrine glands including pituitary were also reported[49]. TCDD affects the pituitary gland by various ways, however, information on toxicity of other industrial solvents is wanting[93-100].

Testis toxicity

In 1775, an English physician, Percival Pott reported a high incidence of scrotal cancer among chimney sweep workers[101]. One of the key questions most frequently asked from toxicologists investigating testicular toxicity is "does this mean that reproductive function will be affected"[102]. There are several organic solvents which manifest testicular damage in man and experimental animals. DNB (m-dinitrobenzene) is notorious for causing the testicular damage. The metabolism of DNB in testicular cells (by Sertoli cells) is shown in Fig. 3.

Within the testes, members of the cytochrome P_{450} play an important role in solvent metabolism[103]. Chronic exposure to hexane or methyl butyl ketone results in testicular damage[104]. 7,12-dimethyl benz(a)anthracene (DMBA) is a polycyclic aromatic hydrocarbon that causes damage to the testis [105]. 2,5-hexanedione and toxicity of aliphatic hydrocarbon has been studied by several workers[104,106-111]. Spermatozoon is target for reproductive toxicants[112]. The nucleus of spermatozoa may be targeted by reactive chemicals that damage DNA. Reactive oxygen species may alter the membrane function and damage DNA in the nucleus of spermatozoa (Fig. 4).

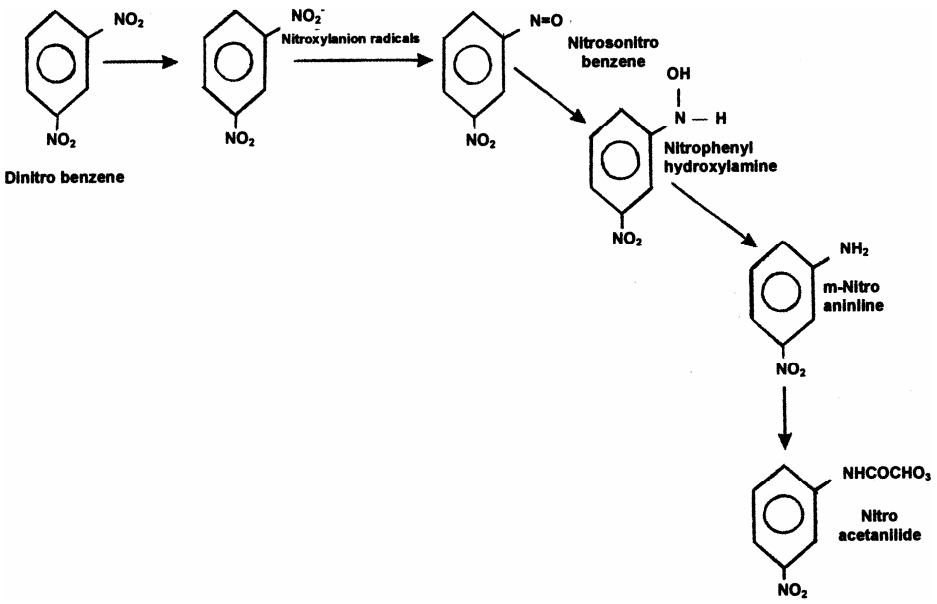

Fig. 3—Metabolism of m-dinitrobenzene by Sertoli cells (ref. 102)

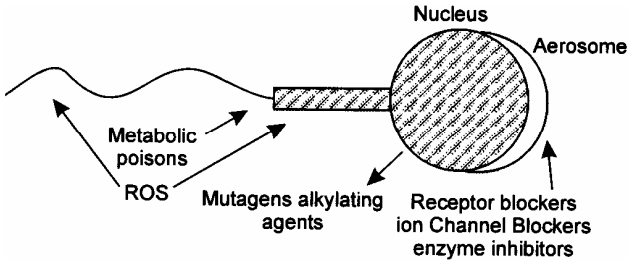

Fig. 4—DNA damage by ROS in the spermatozoon (ref. 112).

Further studies on the testicular toxicity caused by industrial solvents will be important for problems related with human reproduction.

Benzene, toluene and xylene affect the semen quality and function of accessory gland of workers exposed to these chemicals[113]. Co-administration of toluene and xylene antagonized the testicular toxicity[114]. The effect of thinner and its main components, toluene, xylene, methanol and ethyl acetate on testes in male rats was described[115]. n-hexane causes the testicular atrophy in rats[116]. Halogenated compounds (carbon tetrachloride, bromotrichloroethane, carbon tetrabromide, p-bromo benzyl bromide, benzyl bromide) are the potential inducers of lipid peroxidation in rat testis[117]. A known carcinogen ethylbenzene induces the testicular tumor[118]. Benzene induces histopathological lesions in testes[119]. An earlier review described the toxicity of benzene, glycol ethers and carbontetrachloride[120]. Benzene hexachloride also causes the histopathological and biochemical changes in testes[121]. The action of paradicyanobenzene on the testes of mouse was studied[122]. Hexafluoroacetone affect the Leydig cell steroidogenesis and spermatogenesis in rat[123]. Occupational exposure and sniffing of toluene based organic solvents inhibit testosterone synthesis[124]. Toluene also induces the oxidative DNA damage in testes[125]. Trichloroethylene after inhalation causes testicular toxicity in rats[126,127]. Higher concentration of benzene could cause damage to the sperm DNA in industrial workers[128].

Ovary toxicity

The ovaries are target organs for injury caused by many chemicals[129]. The female reproductive system is complex and multifactorial. The ovary is the central component of the hypothalamic pituitary-ovarian axis. It functions cyclically to produce a single oocyte. The follicle is the basic functional unit of the ovary and consists of an immature oocyte surrounded by multiple layers of specialized follicular cells, the theca cells and the granulosa cells[130]. There are various organic solvents which cause damage to the ovaries and its functions. 1-Bromopropane induces ovarian dysfunction in non-pregnant female rats associated with disruption in follicular growth process[131]. Benzene and its analogues affect the luteal function of female workers in petrochemical industries[132]. Ovarian toxicity and carcinogenicity of several

organic compounds viz. 1,3-butadiene, 4-vinylcyclohexane, vinylcyclohexane diepoxide, nitrofurantoin, nitrofurazone and benzene has also been described by Maronpot[133] who reported typical non neoplastic ovarian changes i.e. hyperplasia, atrophy, follicular necrosis and tubular hyperplasia and granulose cell tumors and benign mixed tumors. Benzene fumes also affect the functional activity of ovaries of rats[134]. Dioxin inhibits follicular development[135]. Smoking induces oxidative stress inside the graffian follicle[136]. The effect of chronic inhalation of toluene and dioxane on activity of free radical processes in rat ovaries were also studied[137]. Mixtures of chlorinated alkanes and alkanes consisting of chloroform, 1,1-dichloroethane, 1,1-dichloroethylene, 1,1,1-trichloroethane, trichloro-ethylene and tetrachloroethylene increased the ovary total weights in female ICR mice[138]. Women smokers and women exposed to environmental tobacco smoke containing various organic vapours have reduced ovarian function as evidenced by an earlier menopause, reduced follicular numbers, decreased levels of circulating estradiol and decreased conception rates[139].

Conclusion

Endocrine and hormonally modulated toxicity of xenobiotics have been paid less attention in comparison to other areas of toxicology research. List of chemicals causing primary, secondary and indirect endocrine toxicity hardly mention industrial solvents. Each endocrine gland deserves much more and detailed attention given hitherto. Diversity and complexity of pituitary gland and its interrelationship with brain provide many opportunities for xenobiotics to produce toxicity. Evidence for direct effects of solvents on thyroid and parathyroid glands are also lacking. Pathology of adrenal cortex has been studied but toxicological effects on medulla have rarely been investigated. No major studies have been made to estimate the role of environmental poisons in male reproductive toxicity. Close association between occupational exposure to industrial solvents and infertility necessitates to develop a reliable animal models of testicular dysfunction. Developmental effects of solvents further cause considerable public health concern. Response of endocrine pancreas to toxic injury in terms of apoptosis, necrosis, carcinogenesis, neuroendocrine tumor syndromes, insulinoma, glucagonoma, and multiple endocrine neoplasia syndromes is known for xenobiotics other than organic solvents. In addition, the effects of industrial solvents on cytokines need special attention. To summarize, it is not only the endocrine disruption but endocrine toxicity of industrial chemicals as a whole that needs to be revisited in terms of modern knowledge on hormones and their disorders.

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