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Perspectives in Endocrine Toxicity of Heavy Metals—A Review

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Abstract An attempt has been made to review the endocrine/hormonal implications of a few environmentally significant metals, viz, lead, mercury, cadmium, copper, arsenic and nickel, in man and animals. Special emphasis has been given to the adrenals, thyroid, testis, ovary and pancreas. Toxic metals can cause structural and functional changes in the adrenal glands. Their effects on steroidogenesis have been reviewed. It has been reported that thyroid hormone kinetics are affected by a number of metallic compounds. Occupational exposure to a few of these metals can cause testicular injury and sex hormone disturbances. Protective effects of a few antioxidants on their reproductive toxicity have also been discussed. Information gathered on female reproductive toxicity of heavy metals shows that exposure to these metals can lead to disturbances in reproductive performance in exposed subjects. Certain metals can cause injury to the endocrine pancreas. Exposure to them can cause diabetes mellitus and disturb insulin homeostasis. The need to develop molecular markers of endocrine toxicity of heavy metals has been suggested. Overall information described in this review is expected to be helpful in planning future studies on endocrine toxicity of heavy metals.

Keywords Adrenals · Thyroid · Testis · Ovary · Pancreas · Lead · Mercury cadmium · Reproductive and endocrine toxicity

Abbreviations

c-AMP	Cyclic adenosine monophosphate
ACTH	Adrenocorticotrophic hormone
GH	Growth hormone
TSH	Thyroid-stimulating hormone
PbB	Lead in blood
RAR	Retinoic acid receptor
CNS	Central nervous system
UDP	Uridine phosphate
EPA	Environmental Protection Agency
ROS	Reactive oxygen species
ATSDR	Agency for Toxic Substances and Disease Registry
PGF	Prostaglandin F
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
MT	Metallothionein
HIT-T15	Hamster insulinoma tumour β cells
RIN-m5F	Radiation-induced β cells

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Introduction

A collection of specialized cells that synthesize, store and release their secretions directly in the blood stream is called as an endocrine gland. They respond to changes in internal and external environment in order to maintain the physiological homeostasis. This is regulated by chemical messengers traditionally called as hormones. They include polypeptide hormones, steroid hormones and non-endocrine hormones, i.e. cytokines. Available information on endocrinal implications in toxicity of drugs/xenobiotics suggests that exposure to chemicals/xenobiotics disrupts the endocrine system. A classification scheme to cover main types of endocrine toxicity has been suggested [1]. The primary endocrine toxicity involves the direct effect of drug or chemical on the target gland. Secondary endocrine toxicity occurs where effects can be detected in an endocrine gland as a result of toxicity elsewhere

in the endocrine axis. Many xenobiotics induce toxicity in glands by inhibiting specific enzymes of hormone synthesis pathway. Other compounds manifest toxicity in glands by less obvious mechanisms. Direct toxicity in an endocrine gland can result into hyperfunction or hypofunction of the gland. It can also influence the interactions between endocrine and non-endocrine target tissues. Secondary toxicity is often associated with direct endocrine toxicity.

Heavy metals are known to cause a variety of health problems/diseases/injury, and the mechanisms of their toxicity have been persistently investigated [2–4]. However, endocrinal implications in their toxicity are yet to be explored. While working on toxicological problems associated with heavy metals for last four decades, the need to focus on endocrinal/hormonal involvement in heavy metal toxicity was realized. With this perspective, an attempt was made to review the available information on this area of metal toxicity. In the following paragraphs, toxicity of environmentally significant elements, viz, lead, cadmium, mercury, chromium, copper and arsenic on major endocrine glands, viz, the adrenals, thyroid, parathyroid, gonads, pancreas and placenta has been discussed.

Metals and Adrenal Glands

Adrenal glands constitute two different tissues, differing in development, organization and mode of function. Both the tissues are found throughout the vertebrates, but since their arrangement as medulla and cortex is peculiar to mammals, it is convenient to refer them as chromaffin and adrenocortical tissues. In mammals, the adrenal glands are paired organs situated close to the cephalic pole of the kidneys. The adrenal cortex is mesodermal in origin and secretes steroid hormones derived from cholesterol. Medulla that develops from the neural crest secretes catecholamines. Cortex is regulated mainly by humoural factors where medulla is under the control of splanchnic nerve. Both hormones of cortex and medulla, however, are important in the stress response, and secretions of both the parts are stimulated by stress.

Heavy metals can cause functional stress in the adrenal glands of different organisms. Catecholamine release was reported to be influenced by divalent mercury and cadmium [5]. It was also observed that methyl mercury poisoning impairs adrenal structure and function [6]. The glands were markedly hyperplastic with enlargement of zona fasciculata. Corticosterone levels diminished. In vitro studies demonstrated a defect in conversion of cholesterol to pregnenolone. Fernicola and co-workers [7] reviewed the effects of several heavy metals, viz, Pb, Cd, Hg, Cr, and Mn on the pituitary, thyroid, adrenals, pancreas and gonads. They emphasized the role of CNS centres in the regulation of endocrine function. Cells from zona glomerulosa, zona fasciculata and zona reticularis were isolated, and the effects of Hg, Cd, Co and Cu (100 mM) on their viability were studied [8]. Due to decreased cell viability, there was a parallel reduction in corticotrophin-stimulated corticosterone production by adrenal decapsular cells. The results indicated a direct toxic action by these heavy metals on steroid-producing cells in the adrenal glands. Other metals, viz, Pb, Zn, Al, Cr, Fe, Ni, and Li did not influence the cell viability or hormone-induced steroidogenesis in adrenal glands up to a concentration of 100 mM. Adrenal function in mercury-exposed chloralkali workers was also studied [9]. They reported no significant change in urinary cortisol concentration in 41 chloralkali workers exposed to mercury vapour. The chloralkali workers had a mean urinary mercury concentration of 27 μgm/gm of creatinine. The effects Cd, Hg and Zn on steroidogenesis in dispersed interrenal cells of rainbow trout, *Oncorhynchus mykiss*, were also studied [10]. LC_{50} dose killed 50 % of cells. They concluded that mechanism of toxicity of heavy metals on cortisol-secreting cells involved a site situated downstream from the step generating c-AMP. The same laboratory studied interspecies differences in disruption of cortisol secretion after exposure to Cd [11]. They concluded that endocrine-disrupting effect of Cd is not necessarily related to different levels of metal accumulation but could rather be linked to transport pathways and metal speciation. Cadmium/calcium competition for uptake could be a determinant of the early Cd-induced impaired cortisol secretion in trout but not in perch cells. A recent study showed suppressed adrenocortical responses in birds near a mercury-contaminated river in Virginia [12]. They suggested that Hg may disrupt endocrine system of terrestrial insectivores, the tree swallow nestlings. The mechanisms of the effects of heavy metals on adrenal gland probably involve CNS centres, steroidogenic pathways and regulation of c-AMP, adenyl cyclase and protein kinases (Fig. 1).

Metals and Pituitary-Mediated Effects

Effects of heavy metals on pituitary gland are poorly known. Cd is associated with deleterious effects on gonadal function and with secretory changes in prolactin, ACTH, GH, and TSH [13]. The experimental evidence indicates the existence of a disruption in the regulatory mechanisms of the hypothalamic–pituitary axis. Another report from the same laboratory showed that Cd differentially affects the secretory mechanisms of the pituitary hormones, viz, gonadotropins, prolactin, ACTH, GH and TSH depending upon the dose used (5–100 ppm for 1 month) [14]. The effects on prolactin and ACTH are dose dependent. Several metallic compounds including Zn, Ba, Se, Cd, Hg and Mn did not affect adrenocorticotrophic-hormone-induced steroid production in cultured adrenocortical cells [15]. However, Pb (10^{-5} M) significantly reduced the ACTH-induced steroid production in

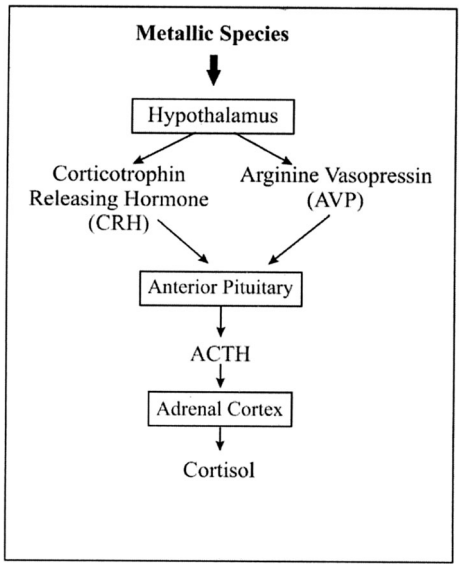

Fig. 1 Interaction of a metal species with hypothalamic–pituitary–adrenal axis

cultured cells. In another study made in a fish, rainbow trout, it was shown that Cd (10–1,000 mM) disrupts the expression of genes critical for corticosteroid biosynthesis in rainbow trout head kidney slices [16]. They proposed that Mc2R signalling is the primary step in ACTH-induced corticosteroidogenesis. It is a key target for Cd-mediated disruption of cortisol production in trout. Caride et al. [17], while studying the chronotoxicity of Cd, suggested that it modifies ACTH and TSH levels around the clock, thus confirming the chronotoxicity at pituitary level.

Thyrotoxicity of Heavy Metals

Evolutionary history of the thyroid gland shows that it is homologous with the endostyle of protochordates and the larval lamprey. In all higher vertebrates, the thyroid develops as a median outgrowth from the floor of the pharynx of embryo. The gland has a unique structure. It consists of follicles of varying sizes that contain colloid produced by follicular cells. These cells are cuboidal to columnar, and their secretory polarity is directed towards the lumen of the follicles. Follicular cells have long profiles of rough endoplasmic reticulum and a large Golgi apparatus in their cytoplasm for synthesis and packaging of substantial amount of protein which are then transported into the follicular lumen. The assembly of thyroid hormones within the follicular lumen is made possible by a unique protein (thyroglobulin) synthesized on the rough endoplasmic reticulum and packaged in the Golgi apparatus of follicular cells. Human thyroglobulin contains complex carbohydrate units with up to four sulphate groups and units with both sulphate and sialic acid. The amino acid tyrosine is incorporated within the molecular structure of thyroglobulin. Iodine is bound to tyrosyl residues in thyroglobulin at the apical surface of follicular cells to form successively monoiodotyrosine (MIT) and triiodotyrosine (DIT). The resulting MIT and DIT combine to form the two biologically active iodothyronines thyroxine (T4) and triiodothyronine (T3) secreted by the thyroid gland in a reaction stimulated by the enzyme thyroperoxidase.

Heavy metals, viz, Cd, Pb, Cr and Cu are known to induce thyrotoxicity in man and animals. Shrivastava and Sathyanesan [18] studied the effect of cadmium on thyroid activity in female palm squirrel, *Funambulus pennanti*. Cd toxicity in the thyroid glands of pregnant rats using electron microscopic X-ray microanalyzer techniques was determined. Serum levels of T3 and T4 were significantly decreased in Cd-treated dams. Marked swelling of the mitochondria was also noticed. This study concluded that accumulation of Cd in mitochondria might disturb oxidative phosphorylation and the loss of energy supply possibly caused by the inhibition of synthesis or release of thyroid hormones [19]. It was also reported that plasma T4 and T3 concentrations in Cd-treated rats were significantly decreased whereas plasma TSH failed to increase in response to low T4 and T3 levels [20]. A report from Poland showed that Cd causes proliferation of calcitonin- and synaptophysin-positive thyroid C cells. A decrease in serum calcium concentration was also recorded [21].

Occupational exposure to lead has been found to affect thyroid function. In a study made in petrol pump workers and automobile mechanics to establish a correlation between blood lead (PbB) levels (2.49+0.45 μmol/L) and T3 and T4 levels, T3 was significantly lower with longer (210 months) exposure in comparison to those having shorter (29 months) exposure. The mean TSH levels were significantly higher in exposed workers in comparison to control group [22]. It was concluded that lead could enhance pituitary release of TSH without having any significant alterations in the circulating T3 and T4. In another study made in China in 157 workers exposed to lead in a smelting factory, it was reported that higher level of PbB (2.88 μmol/L) may cause certain damage to thyroid function by inhibiting deiodination of T4 [23]. Doumouchtsis et al. [24] made an extensive study on the effect of lead intoxication on endocrine functions. They suggested that thyroid hormone kinetics are affected by lead. Central effect is on thyroid axis, or alteration in T4 metabolism or binding to protein may be involved in derangements in thyroid hormone action. Lead toxicity involves alterations in calcitropic hormones homeostasis which increases the risk of skeletal disorders. In a study made on male albino rats, also, it was observed that plasma levels of T3 and T4 are decreased after exposure to lead acetate [25].

Chromium toxicity to the thyroid gland has not been thoroughly studied. Histopathological and biochemical observations in the rat thyroid gland were made after exposure to hexavalent Cr at 30 mg/kg body weight. Results revealed

hyperplasia of thyroid follicles. They were disorganized, clustered and collapsed while a few were fused together. Nuclei were regressed. Colloid retraction within the follicles was noticeable. TSH concentration increased [26]. In another report from the same laboratory, ameliorative effect of vitamin C against Cr-induced thyrotoxicity was demonstrated. Results showed significantly increased TSH and decreased T3 and T4 concentrations [27].

Arsenic and thyroid interactions are also not very well established. However, a few reports from our laboratory show that thyroid status influences effects of arsenic in rat [28]. Another report suggested that hypothyroid fish were more sensitive to arsenate [29]. They concluded that perchlorate enhances arsenate toxicity to juvenile zebra fish and the rate of thyroid recovery after cessation of perchlorate exposure depends upon the end points examined. Arsenic is a potent endocrine disruptor at low and environmentally relevant exposures. Arsenic can disrupt gene regulation via retinoic acid receptor (RAR) or thyroid hormone receptor (TH). Since RAR and TH are critical for both normal human development and adult function and their deregulation is associated with many disease processes, disruption of these processes by As is also potentially relevant to human development problems and disease risk [30].

Not many laboratories have focussed on thyrotoxicity of copper in man or animals. In a report from China, it was demonstrated that administration of copper thiodiazole to Sprague–Dawley rats indicated changes in thyroid end points. T3 and T4 concentrations decreased while TSH concentration increased. It was concluded that thiodiazole copper behaves like a thyroid disruptor in female rat [31].

Relationship between metal exposures and thyroid hormones has been studied by a few workers. A negative correlation between Cd concentration in cord blood and TSH concentration in neonatal blood was observed by a few workers in Japan [32]. Other workers recorded that serum T3 concentration was not affected by Cd, while T4 reduced but only at the exposure to the higher Cd concentration [21]. The influence of thyroparathyroidectomy and that of replacement therapy by T4 on Cu and Zn organ distribution was also examined [33]. These workers concluded that metallothionein could mediate the consequences of thyroparathyroidectomy on metal distribution in liver and kidney. Cadmium treatments have been shown to decrease serum T4 and T3 levels, indicating the adverse effect of long-term Cd intake which increased gradually with duration of treatment [34].

The effect of long-term uptake of mercury on thyroid hormones has also been studied [35]. Recently, Mendy et al. [36] studied lead concentration and thyroid function in American adults. They showed that PbB concentrations were inversely associated with total T3 but were not correlated with thyroid-stimulating hormone, total or free T4, nor free T3. They concluded that PbB may not affect thyroid function.

Mechanisms of thyrotoxicity might involve disturbances in hypothalamic–pituitary–thyroid axis. A metallic species can exert direct effects by disrupting thyroid hormone synthesis/secretion. It may indirectly influence thyroid gland through an inhibition of 5-deiodinase or by inducing hepatic microsomal enzymes, i.e. T4-UDP-glucuronyltransferase. These mechanisms can reduce the circulating levels of T4 and T3 resulting in a release from negative feedback inhibition and increased secretion of TSH by the pituitary gland. The chronic hypersecretion of TSH predisposes the thyroid gland to develop hyperplastic and neoplastic lesions by an epigenetic mechanisms associated with hormonal imbalance (Fig. 2).

Male Reproductive Toxicity of Heavy Metals

Male reproductive disorders that are of interest from environmental point of view include sexual dysfunction, infertility, cryptorchidisms, hypospadias and testicular cancer. Several reports suggest declining sperm counts. However, the male germ line is the most sensitive tissue to the adverse effects of heavy metals.

Testicular toxicity can be caused by any chemical, physical or biological agent that alters physiological control processes and affects the normal function of the testis. A potential gonadotoxic agent can interrupt the normal function of male reproductive system (i) at any level of the hypothalamic–pituitary–testicular axis, (ii) directly at the testicular level or (iii) by altering post-testicular events such as sperm motility or function or both. Several metallic compounds have been known to cause adverse reproductive effects in human and experimental animals. Cadmium is widely spread and extremely toxic. Danielsson et al. [37] reported on accumulation of toxic metals in male reproductive organs. Cd accumulated in the interstitial tissues indicating an effect on hormone production (Leydig cells). Cd has been declared as a testicular toxin [38]. In animal studies, Cd has been shown to cause strain-dependent severe testicular necrosis in mice [39]. Clinical studies have associated Cd exposure with testicular toxicity, altered libido and infertility. Parental or oral exposure to Cd can result in proliferative lesions of the prostate and testis [40]. Subsequent to testicular haemorrhagic necrosis, there will be loss of testosterone, and hyperplasia and neoplasia of testicular interstitial cells are thought to be responses to trophic hormone release from the pituitary. The effects of Cd on testis function were studied also [41]. It was shown that mechanism of toxic effect may involve injury to vascular endothelium, intracellular junctions, germ cells and Leydig and Sertoli cells. The morphological changes induced by Cd included the necrosis of seminiferous tubules and interstitial oedema. It can reduce testosterone synthesis and deteriorate spermatogenesis. Another study reviewed the cellular effects of Cd and showed that Cd induces DNA damage and injury to

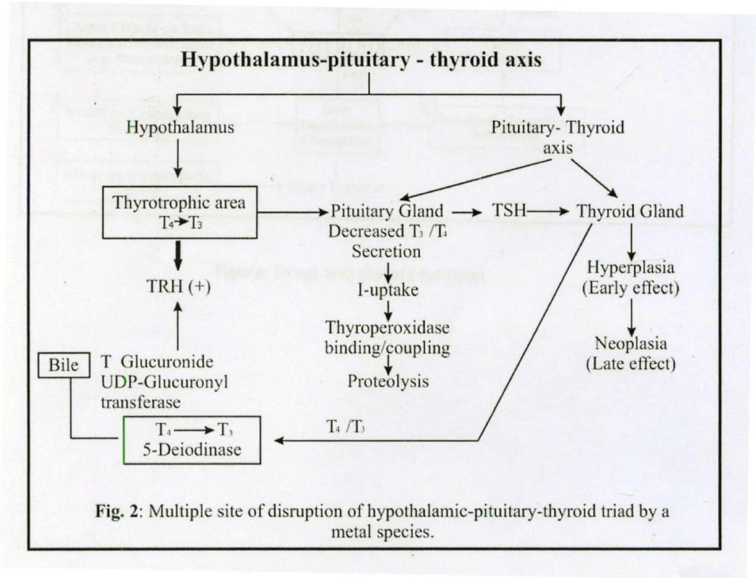

Fig. 2 Multiple site of disruption of hypothalamic–pituitary–thyroid triad by a metal species

membranes and proteins [42]. Different hypotheses on the mechanisms involved in Cd genotoxicity and carcinogenesis were also proposed. Takiguchi and Yoshihara [43] proposed the endocrine-disrupting effect of Cd. It has been known that Cd has potent oestrogen- and androgen-like activities in vivo and in vitro by directly binding oestrogen and androgen receptors. Differential effects of Cd on gene expression in the testis were also studied [44]. They showed that the influence of Cd on gene expression involves a specific effect on LH receptor and not a general effect on transmembrane-spanning receptors. It was also indicated that the increased expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) may be secondary to Cd-induced testosterone deprivation. Thompson and Bannigan [45] described a wide spectrum of deleterious effects on the reproductive tissues and the developing embryo. In the testis, changes due to disruption of the blood testis barrier and oxidative stress were reported. Widespread necrosis at higher dosage exposures was also recorded. Incorporation of Cd in the chromatin of the developing gamete was also demonstrated in their study. It was critically discussed and demonstrated that Cd-induced toxicity in the testis is probably the result of interactions of a complex network of causes. This is supposed to involve the disruption of the blood testis barrier (BTB) vis specific signal transduction pathways and signalling molecules such as p38 mitogen-activated protein kinase (MAPK). Further, other factors such as Cd transporters, metallothioneins and disruption in Zn(2+)- and/or Ca(2+)-mediated cellular events may contribute to endocrinal disrupting behaviour of Cd. Further, it was shown that zinc co-treatment protected testis against toxic effects of Cd [46]. Several reports implicate reactive oxygen species (ROS) in Cd toxicity in the lungs, liver, kidney and testis. However, another study suggested role of oxidative stress in cadmium toxicity and carcinogenesis [47]. Adaptive mechanisms through metallothionein and glutathione were also suggested. Recently, the combined effects of Cd and lead on testicular steroid metabolism and antioxidant system of adult male rats have been studied [48]. Activities of steroidogenic enzymes, i.e. 3-β- and 17-β-hydroxysteroid dehydrogenases, also decreased significantly, leading to altered testosterone production. Metal-exposed groups showed significantly decreased testicular and epididymal sperm count. Cd was more toxic than Pb, while their combined exposure exhibited least toxicity. In vitro experiments showed that vitamin C restores steroidogenic enzyme activities. These observations suggest that Pb- and Cd-induced ROS inhibit the testicular steroidogenesis.

DNA damage caused by Cd, Pb and As in rat germinal cells was also studied. DNA damage (tail length) was measured by comet assay. Significant DNA damage was recorded in primary spermatocytes suggesting a direct testicular toxicity [49].

Strain differences in Cd-induced testicular injury were studied in Wistar Imamichi (WI) and Fischer 344 (F 344) rats [50]. The study concluded that testicular Cd accumulation partly competes with Zn transport system and differences in these systems may play a role in the strain-related differences. In an attempt to establish a relationship between Cd and cancer, it was shown that prolonged exposure to low doses of Cd can induce neoplastic changes in the Leydig cells [49].

Protective effects of a few metals on Cd-induced testicular injury have also been studied. Lithium had a protective effect against Cd-induced testicular apoptosis [51]. The protective effects of Mn against oxidative damage caused by Cd were also examined [52]. This effect was attributed to Mn-induced metallothionein. In a similar study made in metallothionein-III null mice, it was shown that that lack of metallothionein-III (MT-III) contributes to the protection of the testis from Cd

[53]. It was suggested that regulation of purine nucleotide phosphorylase 2 (PNP 2), retinal degeneration (RD3) and cadherin 24 (CDH 24) like mRNA levels may involve the sensitivity of MT-III null mice to Cd. Recently, it was observed that melatonin alleviates Cd-induced cellular stress and germ cell apoptosis in the testis [54]. Melatonin may be treated as a useful pharmacological agent to protect against Cd-induced testicular toxicity.

Testicular injury by Cd in other invertebrate species has also been paid considerable attention. Wang et al. [55] studied Cd-induced oxidative stress and apoptosis in the testis of freshwater crab, *Sinopotamon henanese*. They showed that apoptotic processes may be mediated by mitochondria-dependent pathway by regulating the activities of caspase-3 and caspase-9. Earlier, Jana and Sahana [56] studied the effects of a few metals including Cd on the liver, kidney, testis and ovary of a fish *Clarius batrachus*. In a novel study, protective effects of Cr on the toxicity of Cd were also reported [57].

Toxic effects of chromates in humans have been known for more than 100 years. However, effects of hexavalent as well as trivalent Cr on testicular tissue are poorly known. Murthy et al. [58] observed ultrastructural changes in the form of vacuolization of cytoplasm and degeneration of mitochondria in the epithelial cells. Biological observations in male and female rats exposed to Cr^{III} and Cr^{VI} showed that these compounds would cause adverse effects on fertility and reproduction in mice [59]. The effects of Cr on gene expression in cultured Sertoli cells showed that chromium chloride had modest effects on the expression of many genes in the range of 1.5–2.3-fold [60]. Functional changes in Sertoli cells induced by Cr have also been studied [61]. They studied the uptake and horseradish transport ability of isolated seminiferous tubules of mice administered with Cr^{V} compound. Using in vitro assay, they demonstrated that the seminiferous tubules were able to uptake and transfer the tracer in a much faster way than controls mainly via intracellular and transcellular pathways. Aruldhas et al. [62] studied reproductive toxicity of Cr^{VI} in adult monkeys (*Macaca radiata*). They showed that drinking water containing 100, 200 and 400 ppm of Cr^{VI} disrupts spermatogenesis through oxidative stress while supplementation of antioxidants might be beneficial in affected subjects. The effects of vitamins C and E on the toxicity and mutagenicity of Cr^{VI} in rat and guinea pig have also been studied [63]. The results on the micronucleus test in bone marrow showed that vitamin C produced antimitogenic effect against bichromate in both rats and guinea pigs. Recently, the effects of Cr^{VI} on reproductive functions of male adult rats have been studied [64]. An increase in FSH and a decrease in LH and testosterone serum values were recorded. In addition, significant loss of gametes in the lumen of seminiferous tubules was noted. Histological images showed considerably increased areas filled with seminal vesicles and prostrate secretion.

Available literature shows that both inorganic mercury and organic mercury affect the testis. Mohamed et al. [65] studied the effects of methyl mercury on testicular function in a monkey, *Macaca fascicularis*. In a catfish, *Heteropneustes fossilis*, histopathological lesions were identified after exposure to mercuric chloride [64]. Spermatograms, after treating the fowl with three doses of phenylmercuric chloride (5, 30 ppm Hg; 30 ppm Hg+4 ppm Se) were also evaluated [66]. They showed that treatment with 30 ppm mercury resulted in hypospermia, occurrence of abnormally maturing spermatozoa, reduction of the volume of semen and decrease in the number of spermatozoa. Applied autometallographic enhancement technique was applied to demonstrate the ultrastructural localization of mercury in the interstitial Leydig and Sertoli cells [67]. Chronic effects of methyl mercury were examined through pathological techniques in Wistar rat fed on methyl mercury for 2 years in several tissues including the testis [68]. It was observed that zinc prevented testicular damage produced by mercury in mouse [69]. Mercury-induced alterations in the rat testis showed undulation of basal membrane, dilatation of blood vessels in interstitium and prevalence of empty spaces in germinal epithelium [70]. Problems associated with male reproductive toxicity caused by occupational/environmental/chemical exposures were also addressed [71].

Mechanisms of testicular toxicity caused by mercury have been paid considerable attention. It was concluded that oxidative stress induced by mercury in the testis leads to its toxicity [72]. Loss of antioxidant defence system after mercury exposure may render the testis more susceptible to oxidative damage leading to functional disturbances. These observations were supported by the fact that vitamin E protects against mercurial toxicity in mice [73]. Animals administered vitamin E with mercury showed lower concentration of mercury in the testis and epididymis with partial recovery of sperm and biochemical parameters. Recently, Kalender et al. [74] studied the protective role of sodium selenite and vitamin E against mercurial toxicity in rats. Supplementation of sodium selenite and/or vitamin E to mercury-treated groups declined lipid peroxidation, increased superoxide dismutase, catalase and glutathione peroxidase activities along with milder histopathological lesions.

Occupational/industrial/environmental exposure to lead is a serious public health problem. It is amongst the 200 hazardous substances listed by ATSDR/EPA. Exposure to lead can occur through several occupations, viz, petrol pump operations, printing press, ceramics, glass industry, paints, e-waste and lead acid batteries. Toxicity of lead on male reproductive system has recently been studied [75]. It was shown that lead exposure results in the decline of the reproductive function by inducing oxidative stress, inhibiting enzymes and depleting testicular zinc contents. Another study showed that lead-induced ROS inhibits testicular steroidogenesis, which is

restored by vitamin C treatment [76]. Significant DNA damage was caused by lead in primary spermatocytes of rats [48]. Histopathological attempt to record lead-induced alterations in the testis of rat was also made [77]. A negative effect of lead on the testis was noticed. Lead can induce male reproductive toxicity in a frog *Rana nigromaculata* [78]. They studied malondialdehyde, reduced glutathione and DNA damage in the testis of frog treated with lead nitrate solution at different concentrations from 1 to 1.6 mg/L. Positive correlates were found between DNA damage, malondialdehyde and reduced glutathione levels. Rafuque et al. [79] recorded protective effects of zinc on lead toxicity in the testis. Histopathological observations revealed that Zn prevented toxic effects of lead on germinal epithelium in albino rats. A report from China by Yu et al. (2010) showed that lead exposure decreases serum testosterone concentration but increases inhibin B level. These changes might affect the Sertoli cells [80]. Another report showed the effects of prolonged exposure to lead on seminiferous tubules of rat [81]. Shaban et al. [82] also supported these results showing that low level of vitamin C ameliorates the adverse pathological effects of lead in rat.

Reproductive toxicity of arsenic is not well documented. However, there are a few reports showing testicular toxicity of gallium arsenide indicating spermiation failure [83]. Oxidative stress was suggested to be a major cause of male reproductive failure. As treatment decreased the activity of 3-β-hydroxysteroid dehydrogenase which plays important role in steroidogenesis, the activity could be reversed by co-treatment with ascorbic acid [84]. Gene expression studies were made in TM3 cells, an immortalized Leydig cell derived from the normal mouse testis [85]. This report revealed a concentration-dependent induction of cell proliferation by arsenic. Further, this study provides the evidence that arsenic may play a role in the aetiology of testicular cancer. It was shown that sodium-meta-arsenite-treated mice exhibited dose-dependent gradual reductions in gametogenic cell populations. Leydig cell atrophy was also observed [86]. Recently, Bomhard et al. [87] correlated testicular damage with lung damage caused by gallium arsenide. Li et al. [88] determined gene expression changes in DDX3Y that may be an important target gene of As, and its downregulation may be related to its male reproductive toxicity. Extract of the root of a plant, *Chlorophytum borivilianum*, was also found to exert positive effects against arsenic-induced testicular toxicity [89].

A few workers have shown that metals directly or indirectly influence testosterone production. Recently, the associations between urinary metal concentrations and circulating testosterone in Chinese men were demonstrated [90]. Urinary concentrations of arsenic, cadmium, cobalt, chromium, copper, iron, lead, manganese, molybdenum, mercury, nickel, selenium and zinc and serum testosterone levels were analyzed in 118 men. Their results indicated that elevated Mn and Zn are inversely associated with testosterone production. Earlier, it was established that Cd inhibited the expression of steroidogenic acute regulatory (StAR) protein, which is responsible for the rate-limiting step in steroidogenesis. They showed that Cd can cause a strong induction of testicular PGF(2alpha) production, which might help to explain a well-known antisteroidogenic effect of this heavy metal. Such an inhibitory effect could be due to reduced levels of StAR protein [91]. Another report showed that testosterone pretreatment prevents toxicity of Cd in male C57 mice, possibly through enhancement of MT synthesis [92]. Hosni et al. [93] measured serum levels of FSH, LH, testosterone and prolactin in infertile painters. They observed that infertile painters are at risk of lead-related influence on semen quality, especially sperm motility and increased testosterone level without significant effect on other endocrinal parameters. The effect of chronic mercuric chloride exposure in male rats on reproductive end points thus recorded showed reduced concentration of testosterone in the serum of male rats at a dose that was not clinically toxic [94]. Recently, a dose-dependent increase in blood and testis chromium levels as well as an increase in FSH and a decrease in LH and testosterone levels was recorded [95].

Female Reproductive Toxicity of Metals

Toxins may directly or indirectly affect the ovary [96]. They either might directly alter the cell signalling process of the ovarian cells or may disrupt the hypothalamus–pituitary cell functions resulting in secondary ovarian dysfunction. However, in receptor-mediated events, both sites may be involved and pathogenesis of the lesion may be difficult to define. Classic examples of metals that are known to affect the ovarian function are described here.

Although mercury is known to be a notorious metal, its effects on the ovary are poorly known. Reproductive toxicity of Hg in female rat was studied by Davis and co-workers [97]. It was shown that response to mercury vapour altered oestrous cyclicity but had no significant effect on ovulation, implantation or maintenance of first pregnancy. It was also observed that methyl mercury induced structural chromosomal aberrations and sister chromatid exchange and alterations in reproductive performance in Chinese hamster ovary cells. Reproductive performance of male and female mice was also found to be affected by mercuric chloride [98]. Another study noticed that 0.25–1.00 mg/kg/day of mercuric chloride produced adverse effects on reproductive performance even in the absence of overt mercury toxicity. Fertility and survival indices were significantly reduced in the treated group. In mercury-treated females, weight of the ovary was significantly different from the controls [99]. A report from Al-Saleh et al. [100] indicated that dermal

exposure to mercury can result in a significant accumulation in the ovaries following the application of skin-lightening cream. They concluded that it may cause alterations in reproductive behaviour and contribute to infertility or ovarian failure. Possible involvement of heavy metals, i.e. Pb and Hg, and pituitary hormone FSH in the regulation of progesterone release by procine ovarian granulose cells was also recorded [101].

Female reproductive toxicity of Cd has also been studied by a number of workers. A review of recent literature shows that Cd decreased relative volume of growing follicles and increased stroma in the ovary of rat-administered Cd for 5 months. The number of atretic follicles was found to be significantly higher [102] Ultrastructural observations showed undulation of external nuclear membrane and dilatation of endoplasmic reticulum. Mitochondria with altered structure were also observed. In another report from the same laboratory, the effects of cadmium in combination with zinc and selenium on the ovarian structure of Japanese quails were studied [103]. Co-administration with zinc and selenium showed protective effects. Mechanisms of Cd interference with progesterone synthesis in the ovaries of Wistar rats were studied in vivo and in vitro by Zhang and Zia [104]. They showed that steroidogenic acute regulatory protein which delivers cholesterol to the inner mitochondrial membrane is one site at which Cd interferes with progesterone production in cultured rat ovarian granulose cells. Another site was found to be P450 cholesterol side chain cleavage (P450 scc) which conveys cholesterol to pregnenolone. They showed that both the mechanisms were controlled by the c-AMP-dependent pathway. Adverse effects of Cd on follicle development and oocyte maturation were reported by Wan et al. [105]. They showed that follicle growth, differentiation and steroidogenesis were significantly disturbed by 1.2 μg/ml of CdCl2. Cd at concentrations as low as 1 mM significantly decreased the germ cell density in human foetal ovaries [106]. They correlated it with increase in germ cell apoptosis. They demonstrated that Cd at low concentration alters the survival of male and female germ cells in humans. Reproductive toxicity of Cd in a freshwater prawn *Macrobrachium rosenbergii* was also studied [107]. They performed experiments in intact and eyestalk-ablated prawns. In intact prawns, Cd treatment increased gonad-inhibiting hormone (GIH) secretion but decreased gonad-stimulating hormone (GSH) release. Ovarian toxicity of Cd in hen was attributed it to oxidative stress caused by Cd in ovarian tissue by altering the antioxidant enzyme system, lipid peroxidation and apoptosis. Further, a decrease in serum oestradiol and progesterone levels was also reported [108]. A comparative study between H_2O_2-resistant Chinese hamster ovary cells (CHO(R)) and parental cells (CHO(P)) on cytotoxicity caused by Cd, Cr and Hg was made by Tsuzuki et al. [109]. The role of intracellular active oxygen in heavy-metal-induced damage and cytotoxicity was also discussed.

Effect of Heavy Metals on Placenta

Foetal exposure to environmental heavy metals occurs through amniotic fluid, the placenta and the umbilical cord. Placental barrier is not completely impermeable to the passage of harmful substances, i.e. drugs or toxic agents [110]. Heavy metals have been shown to adversely affect placental functions [111]. During pregnancy, the placenta behaves as a very active transporter of essential (calcium, copper, zinc and iron) and toxic elements (cadmium, mercury and nickel) to the developing foetus [112]. Heavy metals can pass through the placenta and eventually accumulate in foetal tissue. In particular, several heavy metals such as lead, mercury and cadmium are known to alter the delicate maternal–foetal balance potentially causing long-term damage to the newborns [113]. Several workers have investigated toxicokinetic and toxicodynamic properties of heavy metals in the human placenta.

Lead can cross the placental barrier by means of passive diffusion [114]. It precipitates along with calcium in the microvilli around the trophoblast [115]. Lead storage in syntiotrophoblast cells seems to be related with reduced cytochrome oxidase activity [116]. Further, it has also been recorded that mercury vapour and methyl mercury easily pass through the placenta using passive transport and amino acid transporters [117]. The toxicity caused by mercury in placenta implies deregulation in hormone secretion, amino acid transfer, oxygen consumption and membrane fluidity. Reports on cadmium show that it accumulates in placental tissues. Metallothionein retains cadmium in placental tissue and prevents its passage to the foetus. Cadmium also affects placental progesterone synthesis, alters trophoblast cell migration and induces early decidualization of human endometrial stroma cells [111]. Foetal growth and development are also known to be affected by cadmium [118].

Implications of Heavy Metals in the Endocrine Pancreas

The pancreas is composed of exocrine and endocrine cells, both of which synthesize and secrete a wide variety of specific protein–peptide hormone from the islet cells and digestive enzymes from the acinar cells. Toxic manifestations overlap the exocrine and endocrine pancreas. This review focuses on the endocrine pancreas.

The pancreatic islets contain four major cell types, i.e. alpha (α), beta (β), delta (δ) and pancreatic polypeptide (PP) cells. The alpha cells synthesize and secrete the hormone glucagon, the beta cell—insulin, the delta cells—somatostatin and PP cells—a 36-amino-acid linear polypeptide of unknown function. The major human disease reflecting islet dysfunction is diabetes mellitus, and therefore, major focus on

toxicological investigations is on β cells, with possible relevance to the aetiology of disease.

It was suggested that a few heavy metals, viz, zinc, arsenic, cadmium, mercury and nickel may play an important role in diabetes mellitus, as environmental risk factors [119]. Toxic effects of Cd on function of the exocrine and endocrine pancreas showed its accumulation in the pancreas and suggested that it changes the gene and protein expression. The expression of MT-I and MT-II was higher in the pancreas after Cd administration [120]. Another report from the same laboratory [121] confirmed that Cd can influence the biosynthesis of insulin but does not induce the gene expression changes.

Relationship between arsenic and diabetes has been paid considerable attention [122]. It has been noticed that within black foot disease (BFD) endemic areas of Taiwan, diabetic mellitus occurs at higher rates. Yen et al. [123] treated HIT-T15 cells with humic acid, arsenic or both. Their results showed loss of cell viability, apoptosis, depletion of ATP, oxidative stress, activation of caspase-3 and reduced insulin secretion. Exposure of INS-I (832/13) cells to low levels of arsenite led to decreased glucose-stimulated insulin secretion (GSIS) in a dose- and time-dependent fashion. Enhanced nuclear factor-erythroid-2-related factors (Nrf2) activity was also observed in arsenite-exposed cells. This study suggested that low levels of arsenic provoke a cellular adaptive oxidative stress response that increases antioxidant levels, inhibits ROS signalling involved in GSIS and thus disturbs β cell function [124]. Earlier report from Mexico [125] showed that sodium arsenite impairs insulin secretion and transcription in β cells. In a study made in pancreatic β cell-derived RIN-m5F cells showed that inorganic arsenic-induced oxidative stress causes pancreatic β cell apoptosis via mitochondria-dependent and ER stress signalling pathways. What makes pancreatic β cells vulnerable to arsenic? This question was addressed in a study made in Nrf2 knockout mice that demonstrated that Nrf2-mediated antioxidant response is critical in pancreatic β cell defence mechanism against acute cytotoxicity of arsenic. They suggested that Nrf2 plays paradoxical role in pancreatic β cell dysfunction induced by iAs [126].

Pathophysiological effects of mercury on the function of β cells remain, more or less, unknown. Chen et al. [127] treated HIT-T15 cells with methyl mercury and recorded that it causes disruption of the mitochondrial membrane potential and release of cytochrome c from the mitochondria to the cytosol and activation of caspase-3. Treatment of these cells with antioxidant *N*-acetylcysteine effectively reversed the CH3Hg-induced cellular responses.

For the first time, it was reported that Ni exposure causes cytotoxic effects on pancreatic β cells [128]. Exposure to RIN-m5F cells to $NiCl_2$ induced distinct signals of mitochondria-dependent apoptosis. In addition, NiCl2 also markedly induced the activation of c-Jun N-terminal kinase (JNK) but not of extracellular-signal-regulated kinase (ERK) 1/2 and p38.

Effect of Heavy Metals on Hormones

Endocrine-disrupting chemicals including heavy metals are known to affect hormone systems by interfering mainly with steroid and thyroid hormones. Therefore, the predominant effects on human health are alterations in the development and growth processes in exposed subjects. It has been reported that plasma concentrations of gonadotropins, prolactin and aderenocorticotropic hormone declined in cadmium-chloride-treated Sprague–Dawley rats [129]. Piasek and Laskey [130] earlier concluded that Cd can directly interfere with hormone production in the ovary. Smida et al. [131] showed that low and high cadmium chloride concentrations exert opposite effects on progesterone synthesis with a biphasic dose response.

Furthermore, several studies reported an association between Hg exposure in humans and serum hormone levels. Serum oestrone and oestradiol levels were positively correlated with blood Hg levels in male as well as females indicating possible induction of female hormones [132, 133]. Occupational exposure to Hg vapour in workers of chloralkali plants was found to be associated with increase in T3/T4 ratio but a decrease in serum-free T3 levels.

Available literature shows that relationship between lead exposure and activity of hormones has been studied by a number of workers. Pb at higher concentrations produced significant decrease in progesterone production by cultured human granulosa cells [134]. Ronis et al. [135] showed that lead causes dose-related suppression in plasma concentration of testosterone accompanied by a significant decrease in plasma LH, elevated pituitary LH content and a decrease in plasma testosterone/LH ratio at the highest dose. However, in female pups, they observed a suppression of the plasma concentration of oestradiol during puberty. In an earlier report, Ronis et al. [9] suggested that Pb affected the hypothalamus–pituitary–gonadal axis at multiple action sites. Male reproductive toxicity of Pb has been studied by Sokol and Berman [14]. In male Wistar rats allowed to take lead acetate in drinking water, a reduction in testosterone concentration and sperm count was noticed. Knowledge on endocrine disruption by heavy metals is still limited [136].

Other Examples of Endocrine Disruption by Heavy Metals

Not only mammals and fish, but also crustaceans, have been the target of heavy metal pollution. Endocrine-regulated processes amongst crustaceans were found to be affected by

Table 1 Summary of mechanisms involved in endocrine toxicity in heavy metals

Gland	Mechanisms	References
Adrenal	Catecholamine release	Hart and Borowitz [5]
		Burton and Meikle [6]
	Disruption of cortisol secretion	Ranyal et al. [11]
	Suppressed cortical responses	Wada et al. [12]
Pituitary	Secretory changes in prolactin, ACTH, GH and TSH	Lafuente and Esquifino [13]
		Lafuente et al. [14]
	Chronotoxicity	Caride et al. [17]
Thyroid	Inhibition of synthesis of thyroid hormones	Yoshizuka et al. [19]
		Singh et al. [22]
	Hyperplasia of thyroid follicles	Mahmood et al. [26]
Testes	Necrosis and infertility	Goyer [39]
	Low spermatogenesis	Bertin and Averbeck [41]
	Inhibition of testosterone synthesis	Nava-Hernandez et al. [48]
		Yu et al. [80]
	Oxidative stress and apoptosis	Wang et al. [55]; Boujbiha et al. [72]
	Ultrastructural changes	Murthy et al. [58]
	DNA damage	Pandya et al. [76]
	Inhibition of steroidogenic acute regulatory protein	Gunnarsson et al. [91]
Ovary	Reproductive failure	Al-Saleh et al. [100]
	Dilatation of ER	Massanyi et al. [102]
Pancreas	Diabetes mellitus	Lei et al. [120]

heavy metals. Rodriguez et al. [137] reviewed these effects and noted that Cd inhibits ecdysone secretion. Cadmium and copper have been shown to interfere with hormones that stimulate reproduction. Several heavy metals were able to induce hyperglycaemia in crustaceans during short times of exposure, while hypoglycaemic response was noted after longer exposures.

Gene expression responses to heavy metals and steroids were also studied [138]. They showed that worms exposed to Cd respond principally by activating the expression of genes encoding stress response proteins.

Cognitive effects of endocrine-disrupting chemicals including heavy metals, viz, lead, mercury and cadmium were also demonstrated [139]. They stipulated that changes in cognitive function are mediated by the changes in hormonal function.

Cadmium-chloride-induced disruption of testicular steroidogenesis in rainbow trout *O. mykiss* was also studied [140]. Their results indicate that one of the side actions of Cd in the signalling steroidogenic pathway is located prior to c-AMP formation.

Biomarkers/Molecular Markers of Endocrine Toxicity of Heavy Metals

Considerable attention has been paid specially in the last decade to monitor the changes induced by exogenous agents in the expression of genes. Despite large data, overall response of endocrine tissue to heavy metals at genome level has not been studied. Detailed information on molecular markers of heavy metals has recently been documented [141]. In a novel study, Dalton et al. [142] confirmed that Cd-induced testicular necrosis is associated with a single major recessive gene named *Cdm* which has now been localized to mouse chromosome (*ChT*)*3*. They demonstrated *Cdm* gene maps between microsatellite markers *D3Mit 110* and *D3Mit 255*. Identification and characterization of *Cdm* gene might enhance our understanding of heavy metal toxicity. Gene expression studies on other metals and that also in endocrine organs need special attention from toxicogenomists.

Conclusion

This can be concluded that knowledge on the endocrinological implications of heavy metals and vice versa is seemingly restricted to a few glands only. Where as a large body of information is available on the testis, glands like parathyroid, thymus and pineal have been paid no or little attention. Toxic elements can affect the endocrine gland through a direct or indirect or through CNS centres and signal transduction mechanisms. Furthermore, recent research data have attributed the endocrine toxicity to free radicals, oxidative stress, apoptosis and gene expression changes. Role of metallothionein(s) is yet

to be established. Different laboratories have employed different models from cultured cells to fish and primates. Species differences do occur in endocrinal effects of toxic elements. Protective effects of antioxidants, viz, vitamins C and E have also been studied. They support the hypothesis that oxidative stress is responsible for the endocrine injury caused by heavy metals. How toxic elements disturb the hormonal homeostasis is yet to be explained. However, all possible mechanisms have been summarized in Table 1. Since environmental contamination by heavy metals is on the rise, it would be appropriate to study their effects on hormonal homeostasis. Molecular markers of their toxicity need to be established.

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