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Review article

Mechanisms of arsenic disruption on gonadal, adrenal and thyroid endocrine systems in humans: A review

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ABSTRACT

Due to its toxicity as a carcinogen and wide distribution in the environment, arsenic (As) exposure in humans is of public concern globally. Many studies have manifested that As exposure induces cancers besides pathological effects in humans. Animal studies showed that chronic As exposure induces serious neurological effects. Based on recent studies, researchers proposed that As, including arsenate (AsV) and arsenite (AsIII), is also an endocrine disruptor. This review discusses the mechanisms of As toxicity on three endocrine systems including gonadal, adrenal and thyroid endocrine systems. Arsenic methylation and oxidative stress are responsible for As-induced disorders of endocrine systems, however, strong binding of AsIII to thiols also play an important role. Some studies showed AsV toxicity on endocrine systems, but mechanistic investigation is lacking. Research is needed to look into their toxicity mechanisms to help cure the illnesses caused by As-induced endocrine system disorders.

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Contents

1. Introduction

Arsenic (As) is a toxic metalloid widely distributed in the environment. Its presence in soil, food, and water leads to unavoidable As exposure in humans. Furthermore, increasing anthropogenic activities have increased As concentrations in the environment, resulting in greater As exposure. With As concentration increasing in the environment, As pollution is considered an worldwide issue, posing a threat to public health (Halder et al., 2012; Sun et al., 2014). Chronic exposure to As results in a series of health problems, including cancers such as kidney, bladder, skin, and lung cancers, and non-cancerous diseases including cardiovascular, peripheral neuropathy, and obstructive pulmonary disease (Table 1). These diseases may be attributed to As-induced immune disorders in humans. Investigators showed that As can damage immune system, rendering them susceptible to pathogenic challenge (Ahmed et al., 2014; Raqib et al., 2009; Soto-Peña et al., 2006). It is known that

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Table 1
Various health problems associated with As exposure.

Target organ	Health problems	References
Cardiovascular	Hypertension Carotid atherosclerosis Ischemic heart disease Vascular disease mortality	Srivastava et al., 2009
Nervous system	Neurobehavioral alterations Encephalopathy Peripheral neuropathy Delirium	Vahidnia et al., 2007
Lung	Lung cancer Obstructive pulmonary disease Interstitial lung disease Bronchiectasis	Guo et al., 2004; Mazumder, 2007
Liver	Liver damage Affect liver enzyme Portal tract fibrosis Cirrhosis	Guha, 2001
Gstrointestinal	Gastrointestinal irritation Haemorrhagic gastrointestinal lesions	Jomova et al., 2011
Kidney	Kidney cancer	Hopenhayn-Rich et al., 1998
Bladder	Bladder cancer	Moore et al., 2002
Skin	Skin cancer Hyperpigmentation Hyperkeratosis	Maloney, 1996

endocrine system modulates the external toxic effects on the immune system (Davis, 1998). Based on recent research, some proposed that As is a potential endocrine disrupting compound (EDC), which has attracted much attention (Davey et al., 2008; Watson and Yager, 2007).

Endocrine system consists of various glands that produce and secrete hormones, which are transported to distant target organs, thereby regulating the metabolism, growth and development in humans (Witorsch, 2002). EDC is defined as an exogenous agent that interferes with the production, transport and metabolism of natural hormones in human body that are responsible for maintaining homeostasis and regulating reproductive and developmental processes (USEPA, 1996). EDC exerts adverse impacts on humans via either mimicking or antagonizing the effect of hormones and/or disrupting the synthesis of hormones and/or hormone receptors (Amaral Mendes, 2002; Mantovani, 2006).

Arsenic is mainly present as inorganic form in terrestrial environment, including arsenate (AsIII) and arsenite (AsV), both are toxic to humans and animals. It is known that AsIII and AsV induce different toxicity, with AsIII having higher toxicity than AsV. AsIII exerts toxicity via three pathways: 1) binding to sulfhydryls thereby impairing proteins and enzymes, 2) causing oxidative stress via production of reactive oxygen species (ROS), and 3) inducing nucleophilicity via depletion of *S*-adenosylmethionine (Kitchin et al., 2003; Sun et al., 2014). With respect to AsV, due to its structure similarity with phosphate, besides its weak interaction with proteins, it can interfere with oxidative phosphorylation by forming an unstable arsenate ester, impacting ATP production. Furthermore, AsV toxicity also results from the oxidative stress caused by AsV reduction to AsIII (Hughes, 2002; Jomova et al., 2011). The effect of As on endocrine system has been investigated for many years, research shows that As disrupts the gonadal, adrenal, and thyroid endocrine systems (Tables 2-1, 2-2 and 2-3) (Bodwell et al., 2006; Ciarrocca et al., 2012; Jana et al., 2006).

These endocrine systems are controlled primarily by three axes, i.e., the hypothalamic-pituitary-gonad (HPG), hypothalamic-pituitary-adrenal (HPA), and hypothalamic-pituitary-thyroid (HPT) axes (Fig. 1; Liu et al., 2010). This review will primarily focus on the toxicity mechanisms of As-induced disruption of these endocrine systems. Such information helps to understand the pathways of As disruption on the endocrine systems and provides important information for therapy-based strategies to cure As-induced endocrine illness. This review discusses various pathways of As-induced toxicity on the three endocrine systems.

2. Arsenic toxicity on gonadal endocrine systems

Gonadal endocrine system plays a crucial role in regulating human reproductive behavior via controlling gonadal hormones from HPG axis (Figs. 1 and 2) (Hoffmann and Kloas, 2010). The HPG axis consists of hypothalamic-pituitary-ovarian (HPO) in females and hypothalamic-pituitary-testicular (HPTT) axis in males, which control the gonadal hormone production (estrogen and androgen) by the ovaries/testicular through a double-level hormonal hierarchy, i.e., gonadotropin-releasing hormone, and the gonadotropins (follicle-stimulating hormone; FSH, and luteinizing hormone; LH). Gonadotropin-releasing hormone is secreted in the hypothalamus, which then circulates to the pituitary gland and stimulates the production and release of gonadotropins (FSH and LH). These gonadotropins, in turn, stimulate estrogen/androgen production by the ovaries and testicular, regulating gonadal gametogenesis in the initiation of gametogenesis, gonadal maturation and spermiation/ovulation (Stafford, 2005).

Earlier investigators examined As toxic effect on gonadal glands via an animal model, and found that As can be accumulated in the gonadal glands and induce inhibitory effect on the gonadal development (Andersen and Depledge, 1994; Shukla and Pandey, 1985; Zaroogian and Hoffman, 1982). In subsequent studies, investigators discovered that As influences one or more sex hormones, and induces inhibition of ovarian steroidogenesis, reproductive disturbance, testicular steroidogenic function and spermatogenesis (Chattopadhyay et al., 1999; Chattopadhyay et al., 2003; Zadorozhnaja et al., 2000).

Table 2-1
The effects of As on gonadal endocrine system.

As species	Exposure time	Experimental material	Toxic effect	Reference
10 mg L^{-1} AsIII	7 days	Female rats	AsIII stimulates progesterone production	Yuan et al., 2012
20–225 μg L^{-1} AsIII	24 h	MCF-7 cell	AsIII disrupts many ER related genes	Davey et al., 2007
0.4–80 μg mL^{-1} AsIII	7–56 days	Female albino rat	AsIII decreases estradiol, LH and FSH levels	Chatterjee and Chatterji, 2010
0.4 mg kg^{-1} AsIII	28 days	Female albino rat	AsIII decreases ovarian Δ5-3β-HSD, 17β-HSD, and activity of peroxidase	Chattopadhyay et al., 2001
0.5 mg kg^{-1} AsV	20 weeks	Female mice	AsV induces mice lesion, and upregulation of ER immunoreactive protein	Waalkes et al., 2000
Drinking water containing As		Women	Chronic As exposure may increase the risk of fetal and infant death	Milton et al., 2005
Drinking water containing As		Girls	As exposure has a negative effect on menarcheal age	Sen and Chaudhuri, 2007
5 mg kg * day^{-1} AsIII	4 weeks	Male rats	AsIII decreases sperm counts, and LH, FSH, testosterone, and testicular levels and inhibits testicular enzymes	Jana et al., 2006
2, 5 μM AsIII	48 h	Human prostate cancer cell line and PC-3 cell	AsIII represses androgen receptor transcriptional level	Rosenblatt and Burnstein, 2009
0–3 mg kg^{-1}	3 weeks	Male mice	AsIII decreases some key enzymes expression	Chiou et al., 2008
<3590 μg L^{-1} AsVexposure	>50 years	Male	AsV impacts the erectile function	Hsieh et al., 2008
As exposure		Male	AsV exposure is associated with infertility	Shen et al., 2013

Table 2-2
The effects of As on adrenal endocrine system.

As species	Exposure time	Experimental material	Toxic effect	Reference
50 μg L^{-1} AsV	46 days	C57BL/6 J mouse	Arsenic elevates serum corticosterone levels, and reduces levels of corticotropin-releasing factor receptor 1 in offspring hippocampus	Martinez et al., 2008
50 μg L^{-1} AsV	58 days	C57BL/6 J mouse	Increases corticotrophin-releasing factor and hydroxysteroid dehydrogenase levels and alters corticosterone secretion of offspring	Caldwell et al., 2015; Goggin et al., 2012
8 μM AsIII	15–180 min	1470.2 cell line	AsIII represses steroid hormone-regulated gene transcription	Barr et al., 2009
0.7 μg L^{-1} AsIII	3 days	Chick embryo	AsIII interferes with hormone receptor binding and disrupts the hormone-mediated gene transcription	Ahir et al., 2013
0–3 μM AsIII	24 h	H4IIE-G2 T/luc cells	MMA(III), the product of arsenic metabolism, can compete with Zn^{2+} ions, disrupting the stability of GR DNA-binding domain structure	Gosse et al., 2014

Similar toxic effects were observed in humans, with ongoing studies manifesting that As has detrimental effect on men and women's reproduction and development (Lindberg et al., 2007; Sen and Chaudhuri, 2007; Shen et al., 2013). Investigators found that As can reduce men's semen quantity and quality (Kim and Kim, 2015; Shen et al., 2013), influence girls' menarcheal age, and cause spontaneous abortion and stillbirth of pregnancy (Milton et al., 2005; Sen and Chaudhuri, 2007).

Arsenic causes a series of reproduction problems via disrupting gonadal endocrine system, thereby understanding its disturbance pathways is the key to cure related illnesses. The toxic mechanisms of As on HPO and HPTT axes will be discussed separately.

2.1. Arsenic toxicity on hypothalamic-pituitary-ovarian axis (HPO)

HPO axis regulates pubertal development and reproductive function in female via the interaction of the double-level hormonal hierarchy. The effect of As on HPO axis received attentions during the process of exploring As toxicity. Chattopadhyay et al. (1999) reported the impact of As on the HPO axis in rats. After exposing rats to water containing 0.4 mg L^{-1} AsIII for 28 days, they observed the levels of FSH, LH and estrogen in the plasma of 8-week old female albino rats significantly decrease in addition to weight loss of ovary and uterus. Chattopadhyay et al. (2003) later confirmed the results and speculated that the alteration in steroidogenic enzyme activity may be responsible for low plasma levels of estradiol (a prevalent endogenous estrogen) while elevation of glucocorticoid level is probably responsible for repressing the secretion of gonadotropins (FSH and LH). Meanwhile, several studies proposed that AsIII exerts toxic effect via mediating estrogen receptor (ERs), which is regarded as the main route of AsIII disruption in gonadal endocrine system.

It is known that ERs, as the members of the nuclear receptor superfamily of ligand-activated transcription factors, control various physiological processes largely through the regulation of gene transcription (Frasor et al., 2003). Much research has attributed the influence of As on estrogen hormone to ERs (Miller et al., 2002; Stoica et al., 2000). MCF-7, the ER-positive human breast cancer cell line, was used to examine ER and its regulation of gene expression in ER-related studies (Levenson and Jordan, 1997). For example, Stoica et al. (2000) showed that after exposure to 7.5–375 μg L^{-1} AsIII for 24 h, ERα concentrations in MCF-7 cells decrease by 50–90% of the control. They also pointed out that AsIII can activate ERα through the formation of a high-affinity interaction with the hormone-binding domain of the receptor (Stoica et al., 2000). Meanwhile, Chow et al. (2004) also manifested that, after 48 h exposure, 150 μg L^{-1} AsIII repressed the mRNA transcription and protein levels of ERα, but AsIII didn't compete with estradiol for ERα binding due to its non-hydrophobic structure. However, those reports examining the effects of As on ER are inconsistent. To illuminate the toxic mechanism, Davey et al. (2007) further confirmed the toxic effect of AsIII on ERα by demonstrating that ERα is not the actual target for AsIII effects. They showed that AsIII disrupts ERα function via other proteins or regulatory pathways, and at non-cytotoxic levels (20–225 μg L^{-1}), AsIII significantly inhibits E2-mediated gene activation of an ER-regulated reporter gene and the native ER-regulated GREB1 gene in MCF-7 cells. Besides, many studies also reported that AsIII disrupts endocrine system via affecting ER-related genes transcription (Chatterjee and Chatterji, 2010; Davey et al., 2008).

Subsequent studies showed that AsIII also causes toxicity to estrogen production by interfering its signaling pathways (Bae-Jump et al., 2008; Chatterjee and Chatterji, 2010; Watson and Yager, 2007). Bae-Jump et al. (2008) found that AsIII inhibits ERα-mRNA and protein expression in endometrial cancer cells through interaction with the MAPK pathway (mitogen-activated protein kinase), which plays a crucial role in regulating various cellular activities including cell growth, differentiation, survival, and death (Chatterjee and Chatterji, 2010). Watson and Yager (2007) showed that As disrupts the estrogen signaling pathways through suppressing the action of estradiol on the uterus and interaction of ERs with some transcription factors (e.g., Sp1, AP-1, and NF-κB). Moreover, Yuan et al. (2012) demonstrated that AsIII stimulates progesterone production via caspase-3 dependent manner, thereby influencing the estrogen. Besides, investigators also found that AsIII can stimulate MAPK-activation in an ER-dependent manner (Huff et al., 2016; Hyzer et al., 2016).

For AsV, Waalkes et al. (2000) reported that it also has significant effects on ERs. They tested the impact of AsV in Swiss female mice by weekly intravenous injection of 0.5 mg kg^{-1} AsV for 20 weeks. The mice showed lesion, proliferation of uterus, and upregulation of ER immunoreactive protein. Besides, AsV-induced methylation is also

Table 2-3
The effect of As on thyroid endocrine system.

As species	Exposure time	Experimental material	Toxic effect	Reference
1 mg L^{-1} AsV	10–30 days	Zebrafish	AsV causes thyroid histopathology in zebrafish	Liu et al., 2006
150 μg L^{-1} AsV	78 h	Bighead carp	AsV elevates the T4 content	Sun et al., 2016
0.1–1 mg L^{-1} AsIII	10 min	In vitro experiment	AsIII inhibits the activity of thyroid peroxidase	Palazzolo and Jansen, 2008
37.5–150 μg L^{-1} AsIII	24 h	Rat pituitary tumor cells	AsIII alters the expression of thyroid hormone receptor response element and the endogenous TR-regulated type I deiodinase gene	Davey et al., 2008
0.1–4.2 mg L^{-1} AsIII	48 h	Zebrafish	AsIII significantly increases T4 levels	Sun et al., 2015
containing 50 mg kg^{-1} AsIII food	11 weeks	Guinea pigs	AsIII significantly increases T3 and T4 levels	Mohanta et al., 2014
AsIII exposure in air		Human	AsIII exposure increases the levels of thyroid stimulating hormone and thyroglobulin, and decreases free T4 and T3 contents	Ciarrocca et al., 2012

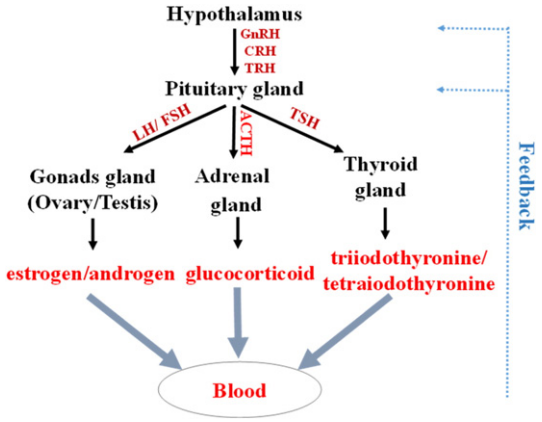

Fig. 1. Relation between different glands in endocrine systems, which consist of gonads, adrenal, thyroid, hypothalamus, and pituitary. Where GnRH = gonadotropin-releasing hormone; LH = luteinizing Hormone; FSH = follicle-stimulating hormone, CRH = corticotropin-Releasing Hormone; ACTH = adrenocorticotropic hormone; GCs = glucocorticoids MCs = mineralocorticoids, CRH = corticotropin-releasing hormone; TSH = thyroid stimulating hormone; T4 = thyroxine, and T3 = thyronine.

associated with abnormal expression of ERα, thereby altering estrogen signaling (Chen et al., 2004; Waalkes et al., 2004).

2.2. Arsenic toxicity on hypothalamic-pituitary-testicular axis (HPTT)

Similar to HPO axis, HPTT axis is responsible for controlling the pubertal development and reproductive function in male via similar double-level hormonal interaction. Based on animal models and epidemiology studies, As exposure causes toxicity in male development and reproductive functions (Pant et al., 2001; Sarkar et al., 2003; Wang et al., 2006). In the 1980s, Shukla and Pandey (1984) showed that AsIII impairs spermatogenesis in freshwater fish (*Colisa fasciatus*) after being exposed to 14 mg L^{-1} AsIII for 30 days. However, their results were not accepted by others. Omura et al. (1996) found that AsIII has no toxic effects on sperm or the testis in rats after intratracheal instillation of 17 mg kg^{-1} AsIII into the trachea of rats. However, Pant et al. (2001) manifested the toxic effect of AsIII on the count, motility and morphological abnormalities in sperm of male mice. They found that the count and motility of sperms significantly decrease and abnormal sperms increase in male mice after feeding water containing

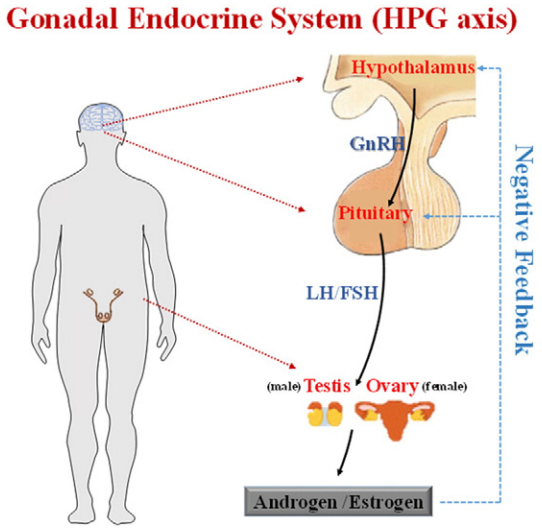

Fig. 2. Relation between different glands in gonadal endocrine system (HPG axis), which consists of gonads, hypothalamus, and pituitary. Where GnRH = gonadotropin-releasing hormone; LH = luteinizing Hormone; and FSH = follicle-stimulating hormone.

40 mg L^{-1} AsIII for 35 days. Jana et al. (2006) exposed male rats to 5 mg kg^{-1} body weight AsIII via drinking water for 4 weeks. They reported decreased epididymal sperm counts and testicular weights, and extensive degeneration of various germ cells. In the subsequent studies, Ferreira et al. (2012) confirmed AsIII toxicity on androgen function based on morphological studies, showing AsIII impairs mice spermatogenesis. Momeni et al. (2012) reported that adult rats show significant decrease in sperm number and mean diameter of seminiferous tubules after orally administering 8 mg kg^{-1} AsIII by gavage for eight weeks, providing compelling evidence for As toxicity on testis.

Considering the high doses used in the previous studies and to better understand the As-induced toxicity mechanisms on male reproduction, subsequent studies used lower As doses. Reddy et al. (2012) demonstrated that the teste weight, seminal vesicle, epididymis and ventral prostate in offspring mice are significantly decreased after exposing mice to 0.4 mg L^{-1} AsIII for 60 days. Meanwhile, Li et al. (2012) manifested that the sperm malformation rate increases while the viability of epididymal spermatozoa and the number of spermatozoa in the testis decrease in rats after AsIII intake of 631 μg during 60 days. These results further confirmed the As toxicity effect on male reproductive function.

After establishing AsIII toxicity on male reproductive function, investigators explored the associated pathway of AsIII toxicity. Researchers found that AsIII's action on male reproduction is similar to that of estrogen. AsIII disrupts androgen by affecting HPTT axis, in other words, AsIII can suppress the release of gonadotrophins (LH and FSH) and testosterone, as well as androgen receptor transcriptional level (Jana et al., 2006; Rosenblatt and Burnstein, 2009; Sarkar et al., 2003). Moreover, Chiou et al. (2008) proposed that the reduction in gene expression of the key enzymes (P450scc, CYP17 and 3β-HSD) in testosterone synthesis is another pathway for AsIII-impaired spermatogenesis. Li et al. (2012) also demonstrated that AsIII can impact maturation of sperms in the epididymis of mice via affecting the expression of Ddx3y gene and protein, which plays an important role during spermatogonia. Besides, AsIII-induced adverse effects through oxidative stress on androgen function cannot be neglected (Jana et al., 2006; Rosenblatt and Burnstein, 2009).

For AsV toxicity, more attentions have been focused on epidemiology studies. Hsieh et al. (2008) reported that chronic exposure to <3.59 mg L^{-1} AsV negatively impacts the erectile function in 177 males who have been drinking AsV-containing well water for >50 years. Xu et al. (2012) reported that As exposure reduces the quality of human semen via a cross-sectional study in China. Shen et al. (2013) also showed that AsV exposure is associated with infertility via analysis of the relation between urinary metabolic biomarkers and semen quality. They observed that AsV-induced oxidative stress may play a partial role in reducing male fertility.

Both AsIII and AsV can disrupt gonadal endocrine system (HPO and HPTT axes) in animals and humans. AsIII-induced methylation and ROS production affect normal expression of gonadal receptors genes (ER and AR). Furthermore, it should be noted that AsIII can affect ER-related genes transcription and some enzymes activity. AsIII's action on male reproduction is similar to its action on estrogenic mode. For AsV, limited research has elucidated the mechanisms for AsV toxicity on HPO and HPTT axes. We speculated that AsV-induced methylation and oxidative stress are responsible for its toxicity during the conversion of AsV into AsIII. More attentions should be paid to examine the mechanisms of how As disrupts gonadal endocrine system.

3. Arsenic toxicity on adrenal endocrine system

Hypothalamus-pituitary-adrenal (HPA) axis (Figs. 1 and 3) controls the corticosteroids (glucocorticoids and mineralocorticoids) production by the adrenal cortex through a double-level hormonal hierarchy, i.e., corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). The CRH is secreted in the hypothalamus, which then circulates to the pituitary gland and stimulates the production

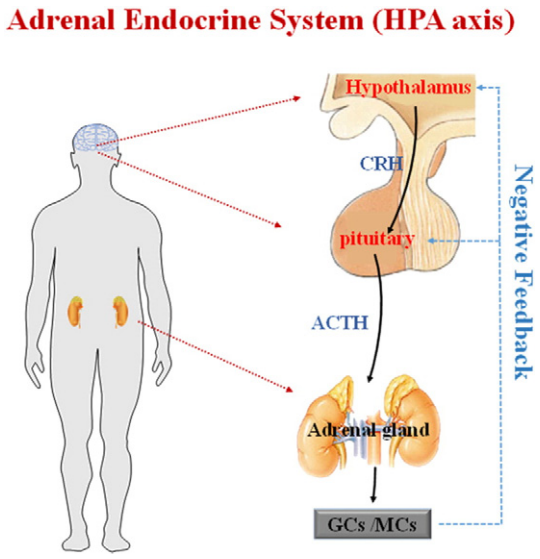

Fig. 3. Relation between different glands in adrenal endocrine system, which consists of adrenal, hypothalamus, and pituitary. Where CRH = corticotropin-Releasing Hormone; ACTH = adrenocorticotropic hormone; GCs = glucocorticoids; and MCs = mineralocorticoids.

and release of ACTH. The ACTH, in turn, stimulates corticosteroid production by the adrenal cortex, thereby regulating the neuroendocrine and behavioral responses in humans. In recent years, numerous studies indicated that As exposure can induce deficiency in cognitive development, learning and memory in mice offspring via HPA axis perturbation (Goggin et al., 2012; Martinez et al., 2008; Xi et al., 2009).

This is because As can interfere with the functioning of key components of the HPA axis. Studies reported that exposure to high AsIII concentration (20 mg L^{-1}) for 9 weeks significantly increases ACTH levels in the plasma of mice. Jana et al. (2006) also found that treatment with 5 mg AsIII/kg body weight per day increases corticosterone level in the plasma of adult male rats and produces changes in dopamine, NE, and 5-HT (serotonin) in both the hypothalamus and pituitary. Subsequent studies explored the AsV toxic effect on HPA axis, demonstrating that lower AsV concentration (50 μg L^{-1}) also affects the HPA axis. Arsenic elevates serum corticosterone levels, reduces levels of corticotropin-releasing factor receptor 1 (a major integrator of adaptive responses to stimulation) in offspring hippocampus, and elevates dorsal hippocampal serotonin serotonin 5-hydroxytrptamine receptor binding (plays an important role in maintaining normal neuronal function) and receptor-effector coupling (Martinez et al., 2008). Some studies also indicated that exposure to 50 μg L^{-1} AsV increases corticotrophin-releasing factor level (the principal regulator of stress response), alters corticosterone secretion and subcellular distribution in the hypothalamus of offspring, and decreases hydroxysteroid dehydrogenase level (play a key role in glucocorticoid synthesis) in pregnant dam and offspring (Caldwell et al., 2015; Goggin et al., 2012). Furthermore, Martinez-Finley et al. (2011) proposed that 50 μg L^{-1} AsV induces GR-mediated transcriptional deficits in the MAPK/ERK pathway, which is an underlying cause of learning and cognitive development deficits. Besides, As-induced abnormal expression of corticosteroid receptors is related to As-induced cognitive deficiency (Martinez-Finley et al., 2009). The corticosteroid receptors are divided into two subtypes of discretely localized receptors, the high-affinity mineralocorticoid receptors (MRs) and the lower-affinity glucocorticoid receptors (Karst et al., 2005).

3.1. Arsenic toxicity on glucocorticoid

It is known that glucocorticoid serves many important roles in human physiological processes by binding to GRs, including consolidation of learned information, stress response glucose and fat metabolism. Though not involved in cognitive development, GRs are implicated to maintain glucocorticoid function (de Kloet et al., 1999; Tsai et al., 2011). Some As-induced diseases such as diabetes mellitus, cardiovascular and cognitive deficits are probably due to the effect of As on GRs. AsIII affects GRs via its high affinity for sulfhydryl groups of proteins by forming stable cyclic thioarsenite complexes with vicinal or paired sulfhydryl group of cellular proteins, thereby disrupting glucocorticoid functions (Simons et al., 1990). This is because AsIII can modify GR activity and effectively blocks steroid binding to GRs via reaction with their vicinal dithiols of unactivated complexes (Lopez et al., 1990). AsIII's impact on glucocorticoids was later confirmed by Kaltreider et al. (2001). They reported that at lower concentrations (22.5–248 μg L^{-1}), AsIII doesn't show toxic effect on cells, instead it interacts directly with GR complexes and selectively inhibits GR-mediated transcription in rat hepatoma cells. Furthermore, they also noted the interaction is associated with altered nuclear function rather than a decrease in hormone-induced GR activation or nuclear translocation.

This valuable information encouraged further research by Bodwell et al. (2004) who discovered the minimal region required for low As levels and proposed that two DNA binding domain cysteines on GR provide one or more binding sites for As, which are identified as peptides 6, 30, 16, 27, 26, and 28 (Kitchin and Wallace, 2006). Barr et al. (2009) found other pathway for AsIII-induced impact on glucocorticoid functions, they manifested that AsIII represses steroid hormone-regulated gene transcription via disrupting the functions of transcriptional coactivators coactivator-associated arginine methylatransferase 1 and glucocorticoid receptor interacting protein 1. Ahir et al. (2013) examined the effect of AsIII on GR and demonstrated that AsIII has a biphasic effect on GR function and disrupts GR-mediated transcription in a complex fashion. They reported that AsIII alters GR's function as a transcription factor and enhances GC induction of endogenous GR-regulated genes at low dose of 0.7 μg L^{-1}, but it interferes with hormone receptor binding and disrupts the hormone-mediated gene transcription by GR at high dose of 7.5 μg L^{-1}. Besides, MMA(III), the product of arsenic metabolism, can compete with Zn^{2+} ions, disrupting the stability of GR DNA-binding domain structure (Gosse et al., 2014; Spuches and Wilcox, 2008). In addition, the oxidative stress caused by AsIII can also activate GR-mediated gene expression via damaging DNA, thereby affecting GR function (Ahir et al., 2013).

3.2. Arsenic toxicity on mineralocorticoid

Like glucocorticoids, mineralocorticoids also play crucial roles in regulating a large number of physiological processes including memory retrieval, visuospatial learning and acid-base homeostasis via binding MRs (Berger et al., 2006; Farman and Rafestin-Oblin, 2001; Martinez-Finley et al., 2009). Thus, abnormal function of MRs would cause multiple health problems. Given the plasma concentration of mineralocorticoids at 0.1 nM, which is <1% of those of glucocorticoids, most studies primarily focused on the AsIII toxic effect on glucocorticoids. Since MR and GR share considerable structural and functional homology, it was assumed that the manners of AsIII toxic effect on MR are similar to those of AsIII on GR. But it is just a speculation and more work is needed to find the accurate manner.

Collectively, both AsIII and AsV disrupt the functions of HPA axis. The effect of AsIII on HPA axis mainly ascribes to AsIII-modified GR activity, which blocks its steroid binding to GRs, while AsIII influences corticosteroid-mediated decrease in GR and MR transcription. Studies revealed that As-induced dysregulation of HPA axis is due to damage on hippocampal, which induces a series of reaction in HPA axis. Only limited documents elucidated the mechanisms of AsV toxicity on HPA axis, so further investigations are needed. Arsenic-induced disruption of adrenal endocrine system is the dominant precipitating factor for diabetes mellitus, and arteriosclerosis and cognitive deficits, therefore,

elucidation of As-induced disruption mechanisms of adrenal endocrine system is useful to cure health issues caused by As.

4. Arsenic toxicity on thyroid endocrine system

Thyroid endocrine system, an important endocrine system in animals and humans, is responsible for releasing and stimulating hormones, which controls the production and release of thyroid hormones (Figs. 1 and 4). Thyroid endocrine system play a crucial role in regulating the dynamics of thyroid hormones, including triiodothyronine (T3) and thyroxine (T4), by coordinating their synthesis, secretion, transport and metabolism (Helmreich and Tylee, 2011; Zoeller et al., 2007). Thyroid endocrine disruptor affects the homeostasis of thyroid hormones via disrupting one or more processes, and As is such a thyroid endocrine disruptor (Ciarrocca et al., 2012; Davey et al., 2008). Regarding As toxic effects on thyroid hormones, lower toxicity of AsV than AsIII originally attracted public interest. Glattre et al. (1995) found that after feeding food containing 175 mg kg^{-1} AsV for 4 weeks, T3 level in Wistar rats increases while the ratio of T4/T3 decreases. However, opposite results were shown in humans. Meltzer et al. (2002) reported that after consuming diet containing 260 μg d^{-1} As for 15 weeks, plasma levels of T3 and T4 in humans are decreased while the ratios of T4/T3 are increased.

These inconsistent results regarding the impact of As on thyroid hormones have stimulated more research. To better assess As risks on humans, investigators studied the As thyrotoxicity via different experimental models. Some research manifested the As thyrotoxicity in fish. Liu et al. (2006) showed that 1 mg L^{-1} AsV causes thyroid histopathology in zebrafish after exposure for 10 or 30 days, i.e., increase in thyroid follicular cell height and decrease in thyroid colloid area. Our recent study also showed AsV thyrotoxicity in the bighead carp larvae, with the T4 content increasing after exposing to 150 μg L^{-1} AsV for 78 h (Sun et al., 2016). To confirm AsV thyrotoxicity in mice, we found that T4 content increases in thyroid tissue impaired mice after oral administering water containing 100 μg L^{-1} AsV for 8 weeks (data not shown). Although there is some evidence confirming AsV thyrotoxicity, more work is needed to understand the associated mechanisms.

Due to higher toxicity of AsIII than AsV, the effect of AsIII garnered more attention. Much effects have been devoted to investigate AsIII-induced thyrotoxicity. Palazzolo and Jansen (2008) proved that after exposure to low AsIII concentrations (0.1–1 mg L^{-1}) for 10 min, the activity of thyroid peroxidase is inhibited in an in vitro experiment, a major enzyme involved in the synthesis of T4 and T3. Davey et al. (2008) showed that exposure to 37.5–150 μg L^{-1} AsIII for 24 h significantly alters the expression of thyroid hormone receptor response element and the endogenous TR-regulated type I deiodinase gene (DIO1) in rat pituitary tumor cells. Thyroid hormone receptor element, specific DNA sequences in target gene promoters, is responsible for TRs regulation transcription by binding with TRs (Aranda and Pascual, 2001). These in vitro results indicated that AsIII affects thyroid hormone levels and disrupts thyroid endocrine system by alternating the expression of TR-related genes.

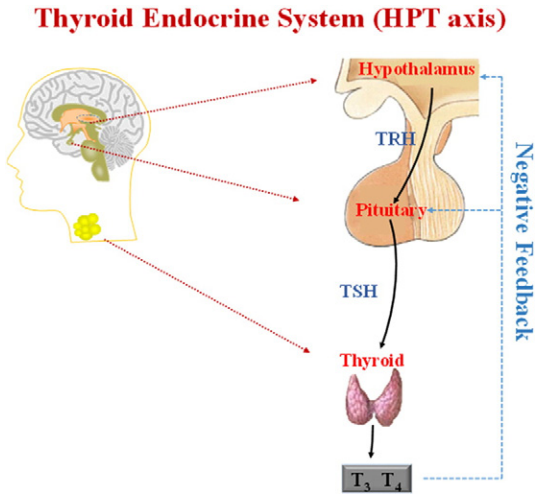

Fig. 4. Relation between different glands in thyroid endocrine system, which consists of thyroid, hypothalamus, and pituitary. Where TRH = thyrotropin-releasing hormone; TSH = thyroid simulating hormone; T4 = thyroxine, and T3 = triiodothyronine.

These in vitro studies provided evidences for additional in vivo experiments. Ciarrocca et al. (2012) reported AsIII thyrotoxicity in humans via residents' health survey. They revealed that higher exposure to AsIII in Italy residents significantly increases the levels of thyroid stimulating hormone and thyroglobulin, and decreases in free T4 and T3 contents, which circulate in blood without bound to thyroid-binding globulin, transthyretion and albumin. Furthermore, pig, as an appropriate surrogate model for human, was used by Mohanta et al. (2014) to assess AsIII thyrotoxicity. They found that the levels of T3 and T4 are significantly decreased in Dunkin Hartley guinea pigs (*Cavia porcellus*) after feeding food containing 50 mg kg^{-1} AsIII for 11 weeks. Besides, our studies also revealed AsIII thyrotoxicity in fish, i.e., AsIII significantly increases the levels of T4 in zebrafish and bighead carp larvae after exposure to 0.1–4.2 mg L^{-1} AsIII for 48 h or 10–150 μg L^{-1} for 78 h (Sun et al., 2015, 2016). Clearly, AsIII thyrotoxicity showed different results in different animals, probably attributing to their different physiological parameters, which may influence As effect on thyroid endocrine system. Though these results confirm the effect of AsIII on thyroid hormones, more work is needed to investigate the associated mechanisms of AsIII thyrotoxicity.

There are sufficient evidences to show As thyrotoxicity, however, limited information is available to explain the mechanisms of As-induced thyrotoxicity. Undoubtedly other glands of thyroid endocrine system also play a crucial role in releasing and stimulating hormones to trigger the production and release of thyroid hormones. Taken together, a better understanding of the effect of As on thyroid endocrine system is needed.

5. Concluding remarks

We discussed As-induced endocrine toxicity and associated mechanisms in humans. Increasing evidences were provided to confirm that AsIII can disrupt gonadal, adrenal and thyroid endocrine systems. It is known that AsIII is chemically more reactive than AsV, binding preferentially to sulfhdryl (SH-) groups, resulting in inhibition of some enzymes and disturbance of some signaling pathways. However, it is worthy to note that low concentrations of AsIII can affect the steroid receptors function, e.g., interferencing ER-mediated gene transcription and influencing GR stabilized structure. Besides, MMA(III) can exert secondary toxic effect, e.g., inhibit ER-GRE (DNA response elements) and GR-GRE binding. The disturbance of AsIII on steroid receptors is a main pathway for AsIII to disrupt gonadal and adrenal endocrine system. Besides, AsIII-induced oxidative stress plays a role in disrupting endocrine systems, though it cannot supplant the role of its direct binding with protein. However, with respect to thyroid endocrine system, available information is limited. Unlike steroid receptors, TRs preferentially bind to their hormone response elements, rather than AsIII. But investigators found that AsIII can disrupt thyroid endocrine system via affecting TR response elements and the expression of type I deiodinase gene, but there are insufficient studies to illuminate the disturbance pathways. It is accepted that thyroid endocrine system regulates the thyroid hormone via a double-level hormonal hierarchy, many enzymes and signaling pathways are involved in the complex process, so AsIII could disrupt one or more steps to induce thyroid endocrine system disorder. More work is needed to further illuminate the accurate mechanism.

Besides, we also found that hitherto few studies reported AsV toxicity on endocrine system. Based on available literature, AsV-induced

Table 3
Abbreviations used in this review.

Chemical	Abbreviations
Arsenic	As
Arsenite	AsIII
Arsenate	AsV
Endocrine disrupting compound	EDC
Hypothalamic-pituitary-gonad	HPG
Hypothalamic-pituitary-adrenal	HPA
Hypothalamic-pituitary-thyroid	HPT
Gonadotropin-releasing hormone	GnRH
Luteinizing hormone releasing hormone	LHRH
Follicle-stimulating hormone	FSH
Luteinizing hormone	LH
Estrogen receptors	ERs
Estrogen receptor α	ERα
Mitogen Activated Protein Kinase Pathway	MAPK pathway
Androgen receptors	ARs
Glucocorticoid receptors	GRs
Thyroid hormones	THs
Thyroxine	T4
Triiodothyronine	T3
Thyroid hormone receptors	TRs
Thyroid stimulating hormone	TSH

methylation and oxidative stress are responsible for AsV disruption on endocrine systems, however, more work is needed regarding its mechanisms. As an endocrine disruptor, arsenic is important to assess the overall impact of contaminants on human health, thereby developing appropriate risk assessment paradigms to better protect human health from arsenic toxicity. Abbreviations are listed in Table 3.

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