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Chapter 3

The Ovary as a Target Organ for Bisphenol A Toxicity

Anna Ptak, Marta Hoffmann and Agnieszka Rak

Additional information is available at the end of the chapter

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Abstract

The ovary is a hormone-sensitive organ that produces steroid hormones. Recent studies show that bisphenol A (BPA) can affect female reproduction; thus, it is important to identify the possible toxic effects of BPA on the ovary because this organ is indispensable for fertility. This chapter summarises the effects of BPA on the ovary by describing how they directly affect folliculogenesis, steroidogenesis and receptor signalling and how they indirectly affect the expression of adipokines and/or their receptors, which exert endocrine or autocrine functions within the ovary.

Keywords: bisphenol A, ovary, folliculogenesis, steroidogenesis, ovarian cancer, adipokines

1. Introduction

In the human, female germ cells develop during the first trimester of pregnancy, whereas primordial follicles develop between the second and third trimesters. Females are born with an entire lifetime supply of non-proliferating oocytes (primordial follicles) that survive for ~50 years [1]. Folliculogenesis is the process by which immature primordial follicles develop into preovulatory follicles (Graafian follicles). More than 99% of follicles never enter the preovulatory stage; instead, they undergo atresia through cell apoptosis. After ovulation, granulosa and theca cells undergo luteinisation and develop into the corpus luteum (CL). Folliculogenesis and oocyte health depend on ovarian and systemic hormones.

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The cycling ovary comprises follicles and the CL. During steroidogenesis, antral follicles produce oestrogens [principally 17β-oestradiol (E_2)] from androgens [androstenedione (A4) and testosterone (T)], whereas the CL produces progesterone (P_4). This balance can be disrupted by altering the concentrations of oestrogen, androgen and/or P_4 or by affecting the expression of steroid hormone receptors. The ovarian steroid hormone receptors include those for oestrogen (ER), androgen (AR) and P_4 (PR), as well as those for luteinising hormone (LH) and follicle-stimulating hormone (FSH). The endocrine system is disrupted when a hormone can no longer bind its receptor due to a disruption in hormone synthesis or receptor binding (**Figure 1**). Additionally, a disruption in folliculogenesis or CL formation can lead to reproductive disturbances, such as aneuploidy, anovulation, decreased fertility, polycystic ovary syndrome (PCOS) and premature ovarian failure (POF). The overall damage to the ovary and its effects on fertility depends on the type of follicles affected [2].

Hormonal disturbances also underlie ovarian carcinogenesis and oestrogens, androgens, P_4, LH and FSH have been proposed to promote ovarian cancer development [3]. Depending on the cellular origin of the tumour, ovarian cancer can be classified as epithelial, stromal or germinal, with each tumour possessing different histopathological features and clinical outcomes (**Figure 2**). Epithelial cell tumours account for ~80–90% of ovarian malignancies, whereas stromal tumours account for ~8%. The most frequently diagnosed type of stromal tumour is the granulosa cell tumour (GCT).

Previous studies show correlations between women working in graphics and printing industries and increased risk of ovarian cancer [4], as well as between women working in similar industries and ovarian cancer mortality [5]. The increased incidence of ovarian cancers cannot be explained by genetic factors. We believe that environmental factors, such as toxic chemicals, can cause ovarian cancer, but it is very difficult to prove cause and effect.

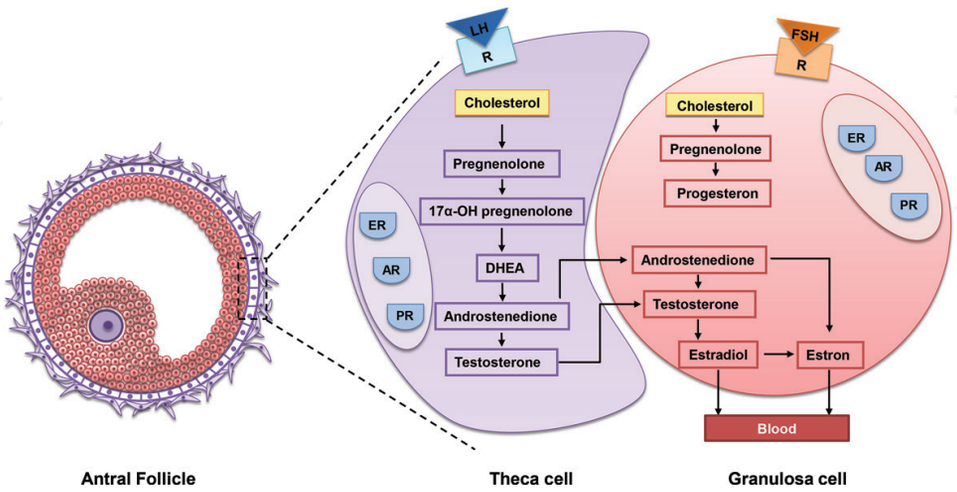


Figure 1. Ovarian steroidogenic enzymes and steroid hormone receptors are targets of endocrine disruption. Oestrogen receptor (ER), androgen receptor (AR) and progesterone receptor (PR), luteinising hormone receptor (LHR) and follicle-stimulating hormone receptor (FSHR) and dehydroepiandrosterone (DHEA).

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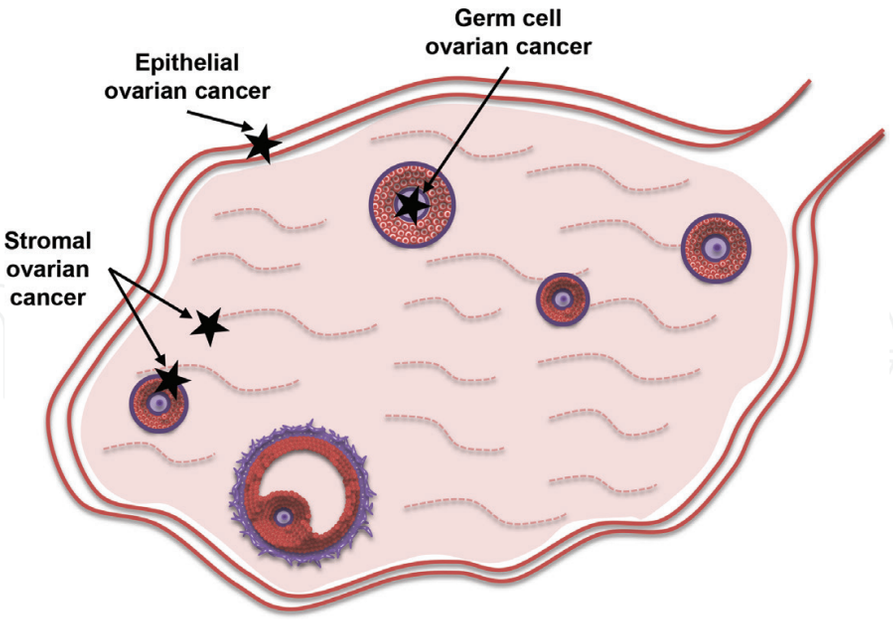


Figure 2. Different types of ovarian cancer. Stars indicate the developmental origins of the tumour.

2. Direct actions of BPA in the ovary

BPA accumulates in reproductive organs and disrupts the endocrine system. In the general population, BPA has been detected in follicular fluid at concentrations of ~1–2 ng/ml [6]. Several epidemiological studies identified correlations between BPA and various abnormalities in the ovary of foetuses and adults. Moreover, the effects of BPA in the ovary, which goes through different stages such as folliculogenesis, ovulation and luteinisation, depend on the time of exposure.

2.1. BPA action on the foetal and neonatal ovary

BPA affects oogenesis and follicle formation during foetal and early postnatal periods. For example, BPA disrupts chromosome segregation during the first meiotic division in the foetal rhesus monkey ovary. During follicle formation, BPA increases the number of multiple oocyte follicles (MOFs), which occurs when more than one oocyte is surrounded by a single layer of granulosa cells [7]. BPA also disrupts meiosis and oogenesis in the foetal mouse ovary, thereby increasing the risks of synaptic abnormalities and aneuploidy [8]. BPA also inhibits germ cell nest breakdown in the foetal mouse ovary by altering the expression of apoptotic proteins, which can lead to various fertility problems and higher percentage of dead pups [9].

Exposure of rats to BPA during the early postnatal period decreases the primordial follicle reserve and increases the incidence of MOFs [10, 11]. In the neonatal mouse ovary, BPA promotes the transition of primordial follicles to primary follicles and suppresses the meiotic maturation of oocytes due to abnormal spindle assembly during meiosis I [12]. Additionally, exposure of rats to BPA during gestational and neonatal periods induces the development of

PCOS-like syndrome during adulthood [13–15]. PCOS is the most common endocrinological pathology in women of reproductive age. It is characterised by hyperandrogenism, insulin resistance and chronic anovulation.

2.2. BPA action on the adult ovary

Oocyte abnormalities were noted in adult mice exposed to BPA, possibly due to changes in the structural integrity of microtubules that constitute meiotic spindles [16]. BPA also disrupts meiotic maturation, spindle organisation and chromosome alignment and increases oocyte degeneration in human oocytes [17].

BPA affects ovarian steroidogenesis by modulating the expression of key steroidogenic enzymes. For example, BPA decreases aromatase (*CYP19A1*) expression and E_2 production in human granulosa cells [18]. In mice, BPA inhibits P_4, testosterone (T) and E_2 synthesis by decreasing the expression of steroidogenic acute regulatory protein (*Star*), 3β-hydroxysteroid dehydrogenase (*Hsd3b1*) and 17α-hydroxylase (*Cyp17a1*) [19]. In rats, however, BPA increases P_4 and T synthesis, as well as the expression of *Star*, cholesterol side-chain cleavage enzyme (*Cyp11a1*) and *Cyp17a1*, but decreases E_2 synthesis and *Cyp19a1* expression [20]. In pigs, BPA increases basal and FSH-induced P_4 synthesis, whereas it decreases FSH-induced E_2 synthesis [21] (**Figure 3**).

In vitro studies demonstrated that BPA affects fertility by disrupting E_2 signalling, which is evolutionarily conserved among mammals and indispensable for fertility. E_2 function is mainly mediated by the classical nuclear oestrogen receptors ERα and ERβ. BPA can bind both ERα and ERβ (its affinity is higher for ERβ than ERα) [22], although its binding affinity for both receptors is greater than 1000–10000-fold lower than that for E_2 [23]. Furthermore, BPA can also induce oestrogen-like effects, because BPA elicits rapid responses through non-classical oestrogen signalling that involves the oestrogen-related receptor γ (ERRγ), [24, 25] as well as membrane-associated G protein-coupled receptor (GPR30) [26] (**Figure 3**).

Therefore, we suggest that BPA seems to be uniquely estrogenic in its receptor binding and androgenic in its hormone profile/steroidogenesis influences.

2.3. BPA and ovarian carcinogenesis

The correlation between BPA exposure and ovarian cancer is supported by little evidence. BPA exposure might increase the incidence of ovarian cysts, because women with PCOS possess higher serum BPA levels than healthy women [27]. Furthermore, women with PCOS have approximately twofold to threefold increased risk of endometrial and ovarian cancers [28, 29]. BPA might also increase the incidence of other ovarian pathologies that ultimately lead to cancer.

The balance between cell proliferation and apoptotic resistance is closely linked to cancer, and it is generally accepted as one of the major contributing factors to cancer development. BPA increases the proliferation of human epithelial ovarian cancer BG-1 [30] and OVCAR-3 [31] cells. The mitogenic effects of BPA are mainly mediated by the upregulation of genes

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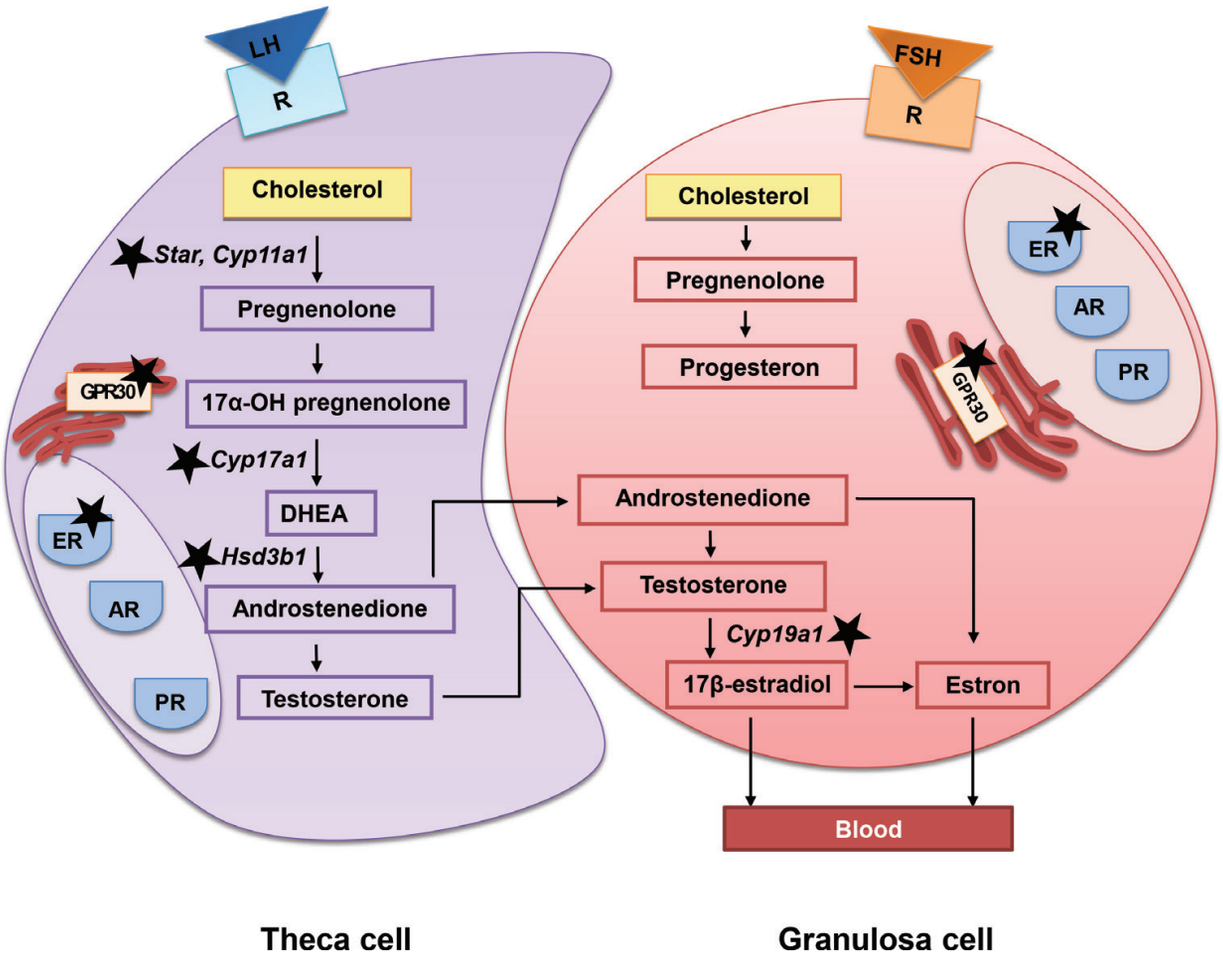


Figure 3. BPA action on ovarian steroidogenesis. Stars indicate the sites of action. Steroidogenic acute regulatory protein (Star), cholesterol side-chain cleavage enzyme (Cyp11a1), 17α-hydroxylase (Cyp17a1), 3β-hydroxysteroid dehydrogenase (Hsd3b1), aromatase (CYP19a1), oestrogen receptor (ER), androgen receptor (AR) and progesterone receptor (PR), luteinising hormone receptor (LHR) and follicle-stimulating hormone receptor (FSHR), dehydroepiandrosterone (DHEA) and membrane-associated G protein-coupled receptor (GPR30).

that induce cell proliferation (i.e., cyclin D1, cyclin A, CDK4, PCNA, E2F1 and E2F3) and the downregulation of genes that inhibit cell proliferation (i.e., p21, Weel-1 and GADD45α) in OVCAR-3 cells [31]. These findings are intriguing because decreased p21/WAF1 expression in ovarian cancer patients is an indicator of poor prognosis [32]. Furthermore, downregulation or inactivation of CDK inhibitors, such as p21Waf1/Cip1, p27Kip1 and p16Ink4a, which renders cells susceptible to extracellular signals that control proliferation, is often observed in various tumours [33]. BPA-induced cell proliferation triggers a rapid biological response involving the phosphorylation of extracellular signal-regulated kinases (ERK1/2), signal transducer and activator of transcription 3 (STAT3) and protein kinase B (AKT) in BG-1 and OVCAR-3 cells [30, 34]. BPA also inhibits OVCAR-3 cell apoptosis by activating ERK1/2 signalling [35] (**Figure 4**).

During tumourigenesis, cells can separate from the primary tumour to invade distant organs. Metastatic cancer cells undergo an epithelial-to-mesenchymal transition (EMT), which is

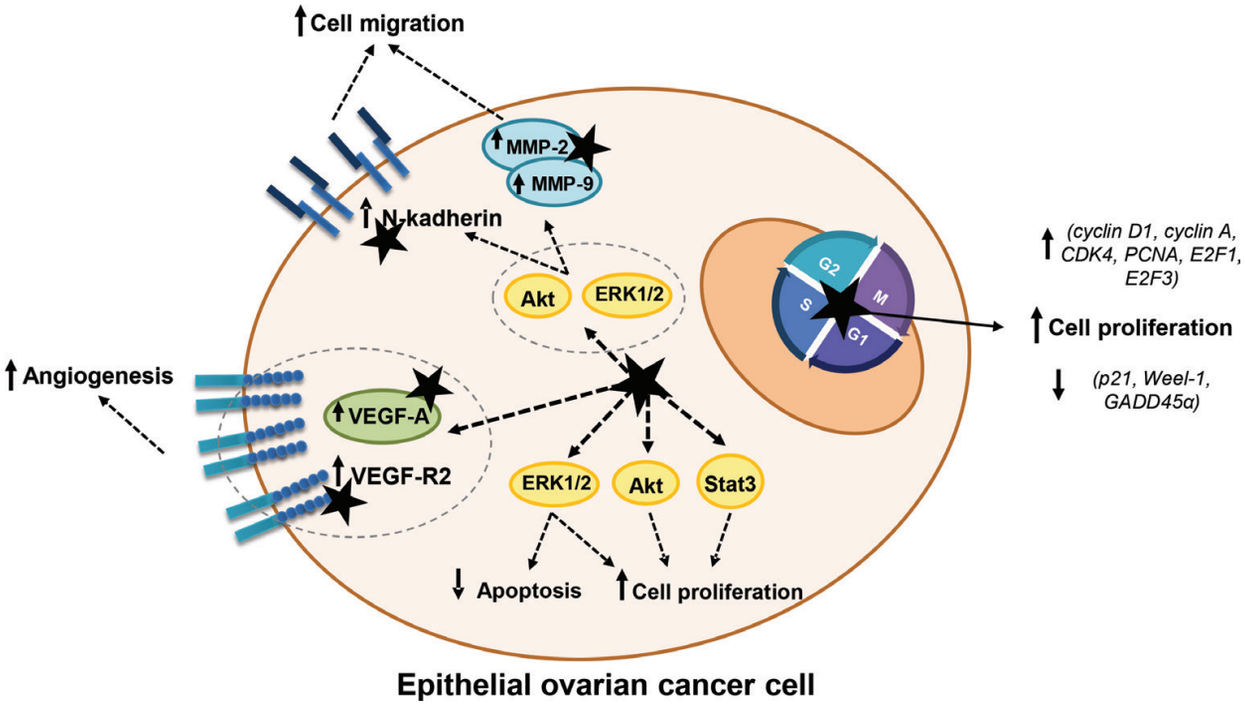


Figure 4. BPA action on epithelial ovarian cancer progression. Stars indicate the sites of BPA action. The arrow facing up indicates a stimulation, and the arrow facing down indicates an inhibition by BPA. Matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor receptor 2 (VEGF-R2), extracellular signal-regulated kinases (ERK1/2), signal transducer and activator of transcription 3 (STAT3) and protein kinase B (Akt).

characterised by the upregulation of mesenchymal proteins such as N-cadherin, downregulation of epithelial cell-associated proteins such as E-cadherin and overexpression of matrix metalloproteinases (MMPs). MMP-2 and MMP-9 are the key enzymes required for the initial steps of ovarian cancer metastasis [36, 37]. In OVCAR-3 cells, BPA upregulates MMP-2, MMP-9 and N-cadherin expression by activating ERK1/2 and AKT signalling, which promotes cell migration [38] (**Figure 4**).

Vascular endothelial growth factor-A (VEGF-A), which is upregulated in most solid tumours, including ovarian cancers, correlates with tumour progression and poor prognosis [39, 40]. Several studies show that the serum VEGF-A level is higher in patients with ovarian cancer than in healthy individuals [41–43]. In addition, the expression of VEGF-A and its receptor (VEGF-R2) is higher in cancerous ovarian tissues than in benign or normal ovarian tissue [44]. BPA upregulates VEGF-A expression in reproductive organs, such as the uterus and vagina in the rat [45] and the ovary in the pig [46]. Moreover, BPA markedly increases VEGF-A and VEGF-R2 expression in OVCAR-3 and SKOV-3 cells [47], indicating a possible intensification of pro-angiogenic activity in ovarian cancer cells (**Figure 4**).

These findings indicate that BPA promotes the progression of epithelial ovarian cancer by stimulating epithelial cell proliferation and migration and inhibiting apoptosis. However, there is no evidence to indicate that BPA affects stromal- and germinal-derived ovarian cancers.

3. Indirect actions of BPA in the ovary through adipokines

Leptin, apelin, chemerin and adiponectin are adipokines that are mainly produced by adipose tissues, but also by other tissues. Adipokines and their receptors are expressed by cells of both the normal and cancerous ovary in humans and other mammals. They play important roles in metabolic processes, such as in the regulation of insulin sensitivity, food intake, adipogenesis and inflammation. Adipokines also regulate ovarian function, including steroidogenesis and oocyte maturation. They also affect ovarian cancer cell proliferation, apoptosis, tumour invasion and angiogenesis.

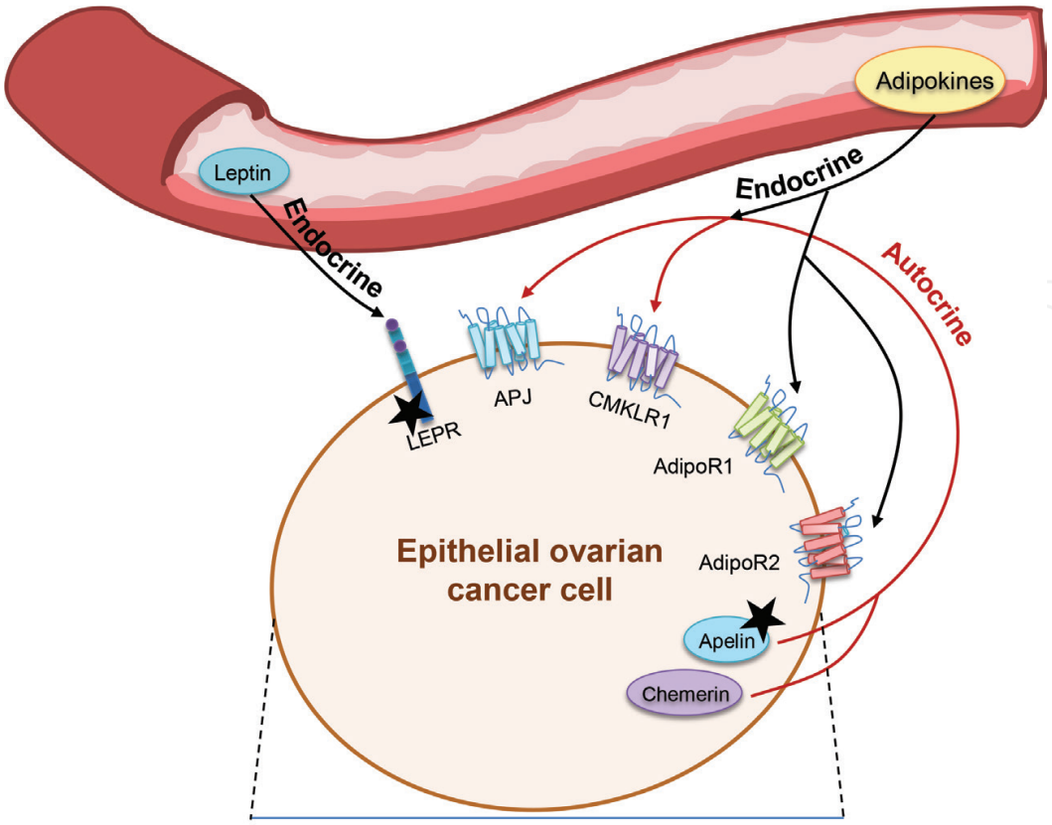
The first discovered adipokine is **leptin**, a 167-amino acid protein encoded by the *ob* gene. The leptin receptor [LEPR, also referred to as the obesity receptor (Ob-R)] is a single membrane-spanning receptor with six isoforms (Ob-Ra, b, c, d, e and f) resulting from alternative RNA splicing [48]. However, only full-length Ob-Rb can transduce signals into cells. Leptin regulates food intake, energy balance and body weight [49]. For example, there is a strong correlation between the serum leptin level and body fat content; the serum leptin level is higher in obese individuals than in those who are non-obese [50].

Granulosa and theca cells in mammalian ovaries express both leptin and LEPR. Leptin stimulates the production of ovarian steroid hormones by affecting insulin, insulin-like growth factor 1 (IGF-1) and different gonadotrophins in the cow [51–53], pig [54, 55], rodent [56, 57] and human [58–60]. There is a correlation between the serum leptin level and the P_4 concentration during the menstrual cycle in humans, as well as between E_2 and human chorionic gonadotrophin (hCG) levels throughout pregnancy [61].

Additionally, a previous study showed an association between Ob-Rb overexpression and survival in 59.2% of ovarian epithelial cell cancers [62]. OVCAR-3 cells express both long (Ob-Rb) and short (ObRt) leptin isoforms [63, 64], which associate with the progression of ovarian epithelial cell cancers. In vitro studies show that leptin promotes BG-1 and OVCAR-3 cell proliferation [34, 63] and inhibits SKOV3, MDAH2774 and OVCAR-3 cell apoptosis [34, 62]. Moreover, leptin stimulates OVCAR-3 cell migration, which is mediated via the activation of ERK1/2, AKT and STAT3 signalling [65]. Leptin also acts on ovarian cancer cells in endocrine manner because they do not produce leptin [35].

BPA can affect the expression of adipokines. BPA increases leptin mRNA expression in the preadipocyte 3T3-L1 cell line [66] and LEPR mRNA and protein expression in OVCAR-3 cells, which creates more binding sites for leptin [34] (**Figure 5**). BPA and leptin also inhibit the apoptosis of cancerous ovarian cells, indicating that BPA can potentiate leptin action in OVCAR-3 cells [35]. These results suggest that BPA increases leptin activity in cancerous ovarian cells.

Apelin is a bioactive peptide that was originally identified in bovine stomach extracts as the endogenous ligand of the orphan G protein-coupled apelin receptor (APJ) [67]. The apelin level is elevated in obese and insulin-resistant individuals and in those with high insulin levels. Apelin functions in a broad range of physiological processes, including fluid homeostasis, food intake, energy metabolism, cardiovascular function and angiogenesis.



	Proliferation	Apoptosis	Migration
Leptin	↑	↓	↑
Apelin	↑	nd	nd
Chemerin	nd	nd	nd
Adiponectin	nd	nd	nd

Figure 5. BPA action on adipokines and their receptors expression in the epithelial ovarian cancer cells. Stars indicate the sites of BPA action. The arrow facing up indicates a stimulation, and the arrow facing down indicates an inhibition. Leptin receptor (LEPR), orphan G protein-coupled apelin receptor (APJ), chemokine-like receptor 1 (CMKLR1), adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2).

The APJ is expressed by granulosa cells, and both apelin and its receptor are expressed by theca cells in the bovine ovary [68]. Apelin and APJ expression in theca cells are induced by LH, whereas increased APJ expression in granulosa cells associates with follicular atresia [68]. Apelin and APJ expression in mature follicles indicate that the apelin-APJ system is important for follicle selection and dominance in cows [69]. Apelin and APJ immunoexpression have been reported in granulosa and theca cells, as well as in oocytes in human follicles, at different stages of development [70]. Furthermore, apelin promotes ovarian steroid hormone secretion, in particular, P_4, and cell proliferation in pigs [71] and E_2 synthesis in humans [70], indicating that apelin has a direct role in folliculogenesis. A recent in vitro study showed that apelin stimulates rat granulosa cell proliferation; however, apelin inhibits granulosa cell apoptosis via PI3K/AKT signalling [72].

The human KGN cell line, which is derived from granulosa-like tumours, expresses apelin and APJ mRNA and protein [70]. Apelin and its receptor are also expressed by cancerous ovarian epithelial cell lines (OVCAR-3, SKOV-3 and Caov-3), the cancerous granulosa cell line (COV434) and the non-cancerous ovarian epithelial cell line (HOSEpiC). Moreover, the basal apelin concentration in both epithelial and granulosa cancer is 0.4–0.6 ng/ml. At these concentrations, apelin acts as a mitogen in these cells. However, BPA increases apelin expression and secretion only in epithelial cancer cells (**Figure 5**). BPA activates the peroxisome proliferator-activated receptor gamma (PPARγ) and not ERα and ERβ, because the PPARγ antagonist (GW9662) abolished the effects of this environmental toxicant on apelin ovarian expression [73].

Chemerin, also referred to as RARRES2 or TIG2, is secreted as prochemerin, an inactive precursor that is processed into biologically active chemerin [74]. Several isoforms of biologically active chemerin with variable C-terminal amino acids have been characterised by their abilities to bind and activate the chemokine-like receptor 1 (CMKLR1). Chemerin regulates adipogenesis, lipolysis and glucose metabolism.

Human granulosa and theca cells express chemerin and its receptor, CMKLR1. Chemerin reduces IGF-1–induced thymidine incorporation, as well as E_2 and P_4 synthesis, by decreasing the phosphorylation of the IGF-1R beta subunit and MAPK ERK1/2 in cultured human granulosa cells [75]. Similarly, chemerin decreases steroid hormone production and MAPK3/1 phosphorylation, probably through CMKLR1, in cultured bovine granulosa cells. In cumulus-oocyte complexes, chemerin blocks meiotic progression at the germinal vesicle stage and inhibits MAPK3/1 phosphorylation in both oocytes and cumulus cells during in vitro maturation [76]. Chemerin also induces rat granulosa cell apoptosis and suppresses basal, and FSH- and growth differentiation factor-9-stimulated, follicular growth in vitro [77].

Chemerin and its receptor are expressed by KGN cells, where chemerin markedly reduces IGF-1–induced cell proliferation and P_4 and E_2 synthesis [75]. Human cancerous ovarian epithelial cell lines (OVCAR-3 and SKOV-3), cancerous granulosa cell lines (COV434 and KGN) and the non-cancerous ovarian epithelial cell line (HOSEpiC) also express chemerin and its receptor. Moreover, chemerin expression decreases in BPA-treated GCTs (unpublished data). However, there is no information on the roles of chemerin in the development and progression of ovarian cancer and no data on the serum chemerin level in patients with ovarian cancer.

Adiponectin (APN), also referred to as ACRP30 or AdipoQ, is the most abundant secreted protein expressed exclusively by adipose tissue [78]. There are three major APN isoforms, namely, a trimeric low-molecular-weight (LMW) isoform, a hexameric medium-molecular -weight (MMW) isoform and a multimeric high-molecular-weight (HMW) isoform [79]. Adiponectin binds its receptors, AdipoR1 and AdipoR2.

The expression of adiponectin and its receptors has been reported in the ovary of various species, including the rat, chicken, pig, cow and human [78]. Except for the cow, adiponectin expression is absent/low in granulosa and cumulus cells of the mouse, chicken and human. In the bovine ovary, adiponectin expression varies in different cells during development [80].

Furthermore, adiponectin receptors are expressed by oocytes and early embryos of the pig and mouse [81]. In vitro studies report adiponectin to decrease insulin-induced androgen and P_4 secretion in bovine theca cells. In rat, chicken and human cultured granulosa cells, however, adiponectin increases P_4 and/or E_2 secretion in response to IGF-1. Several reports in different species, including humans, indicate that adiponectin can modulate not only granulosa cell steroidogenesis but also the expression of genes involved in ovulation. In the cow, adiponectin decreases insulin-induced steroidogenesis and increases IGF-1–induced proliferation of cultured granulosa cells. Adiponectin does not affect oocyte maturation and embryo development in vitro [82]; however, it stimulates oocyte meiotic maturation and embryo development in the pig [81].

The serum adiponectin level is markedly lower in patients with early-stage ovarian cancer than in healthy women. Adiponectin possesses anti-tumourigenic properties; it can suppress tumour growth and cell proliferation, arrest cell growth and induce apoptosis. AdipoR1 promotes KGN cell survival, whereas AdipoR2 regulates steroid hormone synthesis by activating MAPK ERK1/2 [83]. Furthermore, the AdipoR1 mRNA level was lower in Leghorn chicken cancerous ovaries than in normal ovaries [84], suggesting that adiponectin signalling restricts ovarian cancer progression by suppressing tumour cell proliferation and inducing cell apoptosis.

Human cancerous ovarian epithelial cell lines (OVCAR-3, SKOV-3 and Caov-3), the cancerous granulosa cell line (COV434) and the non-cancerous ovarian epithelial cell line (HOSEpiC) express AdipoR1 and AdipoR2, but not adiponectin. Moreover, the AdipoR1 mRNA level is markedly higher in OVCAR-3, SKOV-3, Caov-3 and COV434 cells than in HOSEpiC cells, whereas the AdipoR2 mRNA level is similar among all tested cell lines. BPA does not affect AdipoR1 and AdipoR2 expression (unpublished data), although it decreases the expression and secretion of adiponectin in 3T3-L1 adipocytes [85]. In cultured porcine ovarian follicles, however, BPA markedly increases the expression and secretion of adiponectin, as well as the expression of its receptors, indicating that this environmental toxicant contributes to ovarian dysfunction in obesity-related disorders (unpublished data).

4. Conclusion

BPA can alter ovarian function through several mechanisms. In this chapter, we have discussed two mechanisms by which BPA alters ovarian function. In the first mechanism, BPA acts directly by reducing oocyte quality after foetal and early postnatal exposure; altering the expression and/or activity of key steroidogenic enzymes required for steroid hormone synthesis; binding to steroid hormone receptors and preventing the binding of endogenous ligands; stimulating ovarian cancer cell proliferation and migration; and inhibiting cell apoptosis. In the second mechanism, BPA acts indirectly by altering the expression of adipokines and adipokine receptors, which exhibit endocrine and autocrine actions in ovarian cells. Further studies are needed to understand the effects of BPA on the ovary and its contribution to ovarian dysfunction, such as decreased fertility, PCOS and carcinogenesis.

Conflicts of interest

The authors declare no conflicts of interest.

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