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Cannabinoids in Gynecological Diseases

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Keywords
Endocannabinoid system · Cannabinoid receptors · Endometriosis · Cervical cancer · TRPV1

Abstract
The endocannabinoid system (ECS) is a multifunctional homeostatic system involved in many physiological and pathological conditions. The ligands of the ECS are the endocannabinoids, whose actions are mimicked by exogenous cannabinoids, such as phytocannabinoids and synthetic cannabinoids. Responses to the ligands of the ECS are mediated by numerous receptors like the classical cannabinoid receptors (CB_1 and CB_2) as well as ECS-related receptors, e.g., G protein-coupled receptors 18 and 55 (GPR18 and GPR55), transient receptor potential ion channels, and nuclear peroxisome proliferator-activated receptors. The ECS regulates almost all levels of female reproduction, starting with oocyte production through to parturition. Dysregulation of the ECS is associated with the development of gynecological disorders from fertility disorders to cancer. Cannabinoids that act at the ECS as specific agonists or antagonists may potentially influence dysregulation and, therefore, represent new therapeutic options for the therapy of gynecological disorders.

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Cannabinoids and the Endocannabinoid System

Cannabinoids: Endo-, Phyto-, and Synthetic Cannabinoids

Since its first description as a multifunctional system 2 decades ago, the endocannabinoid system (ECS) has gained a lot of interest [1]. The ECS comprises enzymes, cannabinoid receptors and their related receptors, and ligands, i.e., the endocannabinoids (eCB), which are synthesized endogenously. Phytocannabinoids (pCB) that are isolated from *Cannabis sativa* and synthetic cannabinoids (sCB) affect the receptors of the ECS as exogenous cannabinoids.

The first eCB that were discovered were N-arachidonoyl-ethanolamine, better known as anandamide (AEA), and 2-arachidonoylglycerol (2-AG) [2–4]. Further endogenous ligands of the ECS are 2-AG ether (noladin ether), N-arachidonoyl dopamine, and O-arachidonoyl ethanolamine (virodhamine) [5–7]. The best investigated eCB are AEA and 2-AG, which are produced "on demand". They are triggered by a stimulus that leads to an increase in the intracellular Ca^{2+} concentration and cleavage of precursor molecules [6, 7]. Synthesis of eCB take place in several tissues and cell types where they are

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catalyzed by specific synthases, such as N-acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) and others [8]. After release, inactivation of AEA and 2-AG occurs promptly by enzymatic hydrolysis of the amide and ester bonds by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [9–13].

More than a 100 pCB have been identified, of which the psychotropic (–)-*trans*-Δ^9-tetrahydrocannabidiol (THC) and the nonpsychotropic (–)-cannabidiol (CBD) are the best studied [14–16]. THC and CBD mediate a broad spectrum of biological actions including analgesic, antiemetic, and anti-inflammatory effects [12–14].

Classical Cannabinoid Receptors

Responses to eCB, but also to pCB and sCB, are mediated by numerous receptors of which cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2) represent the classical cannabinoid receptors. CB_1 and CB_2 are G-protein-coupled receptors and they are involved in many (patho-) physiological processes such as pain, inflammation, cancer, and hypertension as well as neurodegenerative disorders [15]. The expression of the CB_1 receptor in the brain is responsible for the psychotropic effects of THC and other synthetic CB_1 agonists. CB_1 expression has also been found in peripheral organs like the heart, spleen, and endocrine glands as well as in parts of the male and female reproductive systems and the urinary tract, including the ovaries, uterus, testis, prostate, and placenta [16–19]. The second classical cannabinoid receptor, CB_2, is expressed only to a minor degree in the nervous system. It is mainly located in tissues of the immune system including the spleen, tonsils, thymus, and bone marrow as wells as in immune cells such as B cells, natural killer cells, monocytes, neutrophils, and $CD8^+$ and $CD4^+$ T cells [20–22].

ECS-Related Receptors

Besides CB_1 and CB_2, many other cannabinoid-sensitive receptors exist that can be designated as ECS-related receptors. Several studies have emphasized their relationship with the ECS [23–25]. The metabotropic G-protein-coupled receptors GPR55, GPR18, and GPR119 have been demonstrated to be targets of eCB, but also of pCB and sCB, but they have not been categorized as cannabinoid receptors by the International Union of Pharmacology [25–29]. Other families of ECS-related receptors are the nuclear peroxisome proliferator-activated receptors (PPAR) and the transient receptor potential (TRP) ion channels [30–33]. The GPR55 receptor plays an important role in cancer cell behavior. It has been shown by different groups in the last few years that GPR55 is involved in cancer cell proliferation in vitro and/or in vivo in various types of cancers including ovarian, prostate, and skin cancer as well as non-small lung cancer [34–38].

PPAR represent a family of nuclear hormone receptors consisting of 3 isoforms (α, δ, and γ [39]), and they are expressed in many organs including the ovaries, uterus, and prostate [40–42]. Numerous functions have been attributed to these receptors including the regulation of metabolism and energy homeostasis, cell proliferation, and inflammation [43–45]. These effects are mediated by a multitude of endogenous and exogenous ligands, e.g., eicosanoids or plant extracts [46, 47]. Within the last 2 decades, researchers have shown that cannabinoids (i.e., eCB, pCB, and sCB) mediate anti-inflammatory and antiemetic effects also via PPARα and PPARγ receptors [48–53].

The TRP channel superfamily responds to many physical and chemical stimuli, including cannabinoids [54]. TRP channels that cause proliferative effects belong to the 3 major subfamilies of these channels, i.e., the TRPC (canonical), the TRPV (vanilloid), and the TRPM (melastatin) channels [55]. Within the members of these subfamilies the TRPV6 channel is the best studied. A high expression of TRPV6 has been found in many types of cancers, such as colon, thyroid, prostate, and ovarian cancer [56–61]. The TRPC6 channel of the TRPC subfamily and some members of the TRPM subfamily have been shown to be related to procarcinogenic effects in prostate, cervical, ovarian, breast, and gastric cancers [62–67].

(Patho-) Physiological Impact of the ECS

A variety of physiological and pathological processes throughout the organism are affected by the ECS including modulation of neuronal functions, microcirculation, and functions of immune cells [68]. Hence, the ECS takes part in the modulation of pain and inflammation and may be also involved in regulatory processes during carcinogenesis [69–75]. Ligands of the ECS could act via cannabinoid receptors as well as via ECS-related receptors. The receptors represent therapeutic opportunities in the treatment of pain, inflammation, and chemotherapy-induced nausea or vomiting since they cause inhibitory effects in these pathological processes [76]. Aside from that, modulation of the ECS by natural and synthetic ligands may also result in the induction of apoptosis, inhibition of cancer cell invasion, and neoangiogenesis [77–81].

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The ECS in Gynecological Disorders and Cancer

Since the ECS is involved in almost all levels of female reproduction, i.e., from oocyte production to parturition, several studies in recent years have shown that dysregulation of the ECS is associated with the development of disorders of the female reproductive tract [82–90]. These include fertility disorders like polycystic ovary syndrome (PCOS), endometriosis, and gynecological cancers [91–93].

Cannabinoids and PCOS

PCOS is a metabolic and endocrinal disorder. Its pathogenesis was only recently connected to the ECS by demonstrating that levels of AEA and 2-AG were elevated in peripheral blood mononuclear cells of women with PCOS [94]. Recently, Cui et al. [95, 96] found reduced FAAH expression in the endometrium of patients with PCOS and an increase in AEA plasma levels, as FAAH is mainly involved in AEA degradation. Previous studies have shown that elevated plasma AEA levels in connection with a lower FAAH activity resulted in ectopic pregnancy which is also linked to PCOS [85, 97]. Thus, it seems likely that a dysregulation of the ECS is involved in pregnancy complications of women with PCOS.

Apart from high eCB levels, insulin resistance is common in the pathophysiology of PCOS, often causing hepatic stress and liver damage, which ends up in elevated levels of alanine aminotransferase, a marker of hepatocellular injury. Dawson et al. [91] recently reported that a weight-reducing therapy with the CB_1 antagonist rimonabant in obese women with PCOS resulted in a reduction of alanine aminotransferase, accompanied by a reduction of insulin resistance. In contrast, it has been reported that the amount of both vascular endothelial growth factor and interleukin-8, which play a crucial role in inflammation, are paradoxically increased upon rimonabant treatment of obese women with POCS, which may compensate the benefit associated with weight loss [98]. More data are, therefore, needed to clarify the impact of the ECS in the pathogenesis of PCOS and whether a CB_1 antagonist may be of benefit.

Cannabinoids and Endometriosis

Endometriosis is a disease characterized by ectopic growth of uterine endometrial tissue and it is usually associated with severe pain. Since the mechanisms for endometriosis-related pain can be divided into 3 categories (nociceptive, inflammatory, and neuropathic), each of which is linked to the ECS, it is not surprising that the ECS represents a big field of research for the development of new therapeutic tools in the management of this disorder. Sanchez et al. [99] recently reported elevated plasma levels of AEA and 2-AG in women with endometriosis. There were, however, no changes in CB_1 expression in endometrial stromal cells during the menstrual cycle of the women with endometriosis, although in the healthy controls (and in contrast to findings by Bilgic et al. [100]) an upregulation of CB_1 was found in the S-phase [99]. TRPV1, an ECS-related receptor, was found to be expressed at comparable levels in ectopic endometrial stromal cells from both healthy controls and women with endometriosis [99]. These findings are in accordance with previously published studies showing TRPV1 expression in ectopic endometrial epithelial cells [101]. The presence of this receptor in endometrial tissue and the elevated levels of eCB in patients with endometriosis may therefore be associated with the development of chronic inflammatory pain [99].

Besides the discovery of new treatment targets for pain management, there is still the need to know how ectopic lesions develop and proliferate. By immunostaining of CB_1 and CB_2 in endometriotic and normal tissue, Bilgic et al. [100] showed that the expression of both receptors was reduced in the glandular epithelial and stromal cells of women with endometriosis. This is in agreement with findings by Resuehr et al. [88], who observed reduced immunostaining of CB_1 in patients with endometriosis [88, 100]. Moreover, it was demonstrated that the selective CB_1 agonist ACPA as well as the selective CB_2 agonist CB 65 induced apoptosis and reduced proliferation of Ishikawa cells (normal endometrial glandular cells) and the endometriosis cyst wall cells CRL-7566 [100]. The CB_2-mediated effect was more prominent in Ishikawa cells while the CB_1-mediated effect was more prominent in CLR-7566 cells [100]. Similar results were presented earlier by Leconte et al. [102], who demonstrated an antiproliferative effect of the nonselective CB_1/CB_2 agonist WIN 55212-2 on deep infiltrating endometrial stromal cells. This effect was a result of inactivation of the Akt pathway by WIN 55212-2 [102]. These in vitro results were confirmed by a mouse model of deep infiltrating endometriosis [102]. In contrast, Sanchez et al. [103] found that selective activation of CB_1 by methanandamide was linked to the development of ectopic lesions in a mouse model of endometriosis. The discrepancies may be explained by the fact that there are basic differences in the animal models of endometriosis. Sanchez et al. [103] used a model to elucidate the development of ectopic lesions in initial stages while Leconte et al. [102] transplanted human endometriotic tissue into nude

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mice to investigate effects on already established lesions. Thus, species differences between the rodent and human endometrium may exist [102, 103]. Certainly, more research is necessary to identify potential new targets for therapy of endometriosis.

Cannabinoids and Cervical Cancer

Cervical cancer is the second leading cause of cancer in women and, due to the lack of effective treatment, more than 250,000 deaths are reported annually [104]. A possible influence of the ECS in the development of cervical cancer has been elucidated in recent years. Contassot et al. [89] reported a strong expression pattern of CB_1 and CB_2 as well as TRPV1 in cervical carcinoma cell lines and biopsies. On top of that, it was shown that AEA had proapoptotic effects on cervical carcinoma cell lines (HeLa and Caski) [89], which were not inhibited but rather enhanced by CB_1 and CB_2 antagonists. On the other hand, the TRPV1 selective antagonist capsazepine protected the cell lines from AEA-induced apoptosis, indicating an important role of the TRPV1 channel in the proapoptotic action of AEA [89]. Additionally, it was demonstrated by Ramer et al. [105] that CBD is able to decrease the invasiveness of cancer cells in a concentration-dependent manner. The effect was observed in the cervical cancer cell lines HeLa and C33A as well as in the lung cancer cell line A549 and seemed to be mediated by the upregulation of TIMP-1 via CB_1/CB_2 and TRPV1. The activation of p38 and p42/44 mitogen-activated protein kinases was identified as an upstream event of TIMP-1 upregulation [105]. In agreement with these findings, it was reported that treatment of different cervical cancer cell lines (HeLs, SiHa, ME-180) with CBD led to a decrease of cell proliferation [106]. Furthermore, CBD induced cell death by the accumulation of cells in the sub-G_0 phase (cell death phase) of the cell cycle, a finding that was most likely caspase dependent because caspase-9 as well as caspase-3 were upregulated upon CBD treatment [106]. Hence, CBD may be an additional therapeutic tool for the treatment of cervical cancer, but in vivo studies will be needed to exactly clarify the impact of CBD on cervical cancer.

Cannabinoids and Ovarian Cancer

Among gynecological cancers, ovarian cancer is responsible for the highest mortality rate [107]. To determine a possible role of the ECS in the pathophysiology of the ovaries, El-Talatini et al. [82] studied the expression levels of different components of the ECS [108]. They were able to show the expression of CB_1 and CB_2 as well as of NAPE-PLD and FAAH in normal human ovaries by immunohistochemical methods. Additionally, they found AEA in the follicular fluid after ovarian stimulation by hormones (following an in vitro fertilization protocol which caused an increase in follicle size), suggesting that AEA is involved in the maturation of follicles and oocytes [82, 108]. Another study group demonstrated expression of CB_1 and FAAH in the ovarian surface epithelium from which ovarian cancers originate, which could be another hint for a possible involvement of the ECS in ovarian cancer [109]. The 2-AG degrading enzyme MAGL has been shown to be upregulated in aggressive human ovary cancer cells [110]. MAGL seems to be involved in oncogenic signaling and hence in increased migration, invasion, and survival of cancer cells. This was also demonstrated by MAGL overexpression in nonaggressive cancer cells which subsequently exhibited an increased pathogenic phenotype [110]. Moreover, the application of an MAGL inhibitor led to a reversion of the enhanced pathogenicity [110]. Regarding the expression of CB_1 in ovarian cancer, Messalli et al. [111] revealed, by using immunohistochemistry, that CB_1 expression was moderate in benign and borderline epithelial ovarian tumors, but the expression was strongly increased in invasive ovarian tumors. These findings suggest a correlation between the expression patterns of ECS components and the prognosis for ovarian cancer malignancy [111].

It also turned out that the amount of lysophospholipids in blood and ascites fluids was elevated in ovarian cancer patients compared to healthy controls, a finding associated with proliferation and the metastatic potential of ovarian cancer cells [112]. Hofman et al. [38] more recently described that the elevation of lysophosphatidylinositol (an endogenous GPR55 agonist) in the ovarian cancer cell lines OVCAR-3, OVCAR-5, and COV-362 resulted in a GPR55-dependent angiogenesis because pharmacological inhibition and genetic deletion of GPR55 reduced the proangiogenic potential of lysophosphatidylinositol in these cell lines. Additionally, they demonstrated that the mitogen-activated protein kinase pathway was activated via GPR55 by phosphorylation of ERK1/2 and p38, which are signaling molecules known to be involved in proliferative and migratory responses [38]. Thus, the involvement of the ECS in ovarian cancer may fuel expectations on new therapeutics to combat this type of cancer.

Cannabinoids and Endometrial Cancer

Endometrial cancer can be classified into type I and II tumors. Depending on the disease stage, various therapies exist, but the prognosis is still poor because of tumor recurrence [113]. Guida et al. [114] reported an upregula-

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tion of CB_2 in endometrial cancer, whereby immunostaining was only successful in transformed malignant cells and completely absent in normal endometrial tissue. Furthermore, 2-AG levels were increased but MAGL expression was decreased in comparison to controls, while AEA levels and FAAH expression were unaffected [114]. In accordance with these findings, Jové et al. [115] demonstrated that CB_2 was expressed at higher levels in stages III and IV of endometrial carcinoma, which has been linked to a poor prognosis. Contrary to Guida et al. [114], they found an increase in CB_1 expression by immunohistochemistry in endometrial carcinoma tissue compared to normal endometrial tissue [115].

The effects of pCB, such as THC, on endometrial cancer progression was recently evaluated by Zhang et al. [116]. They found that THC inhibited endometrial cancer cell proliferation and migration by a decreased expression of matrix metalloproteinase-9 but not matrix metalloproteinase-2. The same effects could be detected after matrix metalloproteinase-9 silencing [116]. More recently, the involvement of THC and CBD in endometrial cancer was investigated in 2 model cell lines, i.e., Ishikawa and Hec50co cells [117]. Expression of all components of the ECS, including TRPV1, was detected in the cells. Additionally, treatment of the cells with AEA or CBD (>5 μM) resulted in a reduced cell viability that was linked to an increase in ROS production and caspase-3/-7 activity [117]. The findings regarding the proapoptotic action of AEA are well in accordance with the observations by Contassot et al. [89], who described AEA-driven cancer cell apoptosis via TRPV1 activation.

Conclusions

A pivotal effect of the ECS in gynecological disorders and cancers was demonstrated by various working groups in recent years. In particular, the development, progression and prognosis of female urogenital diseases seem to be associated with dysregulation of the ECS. Due to its regulatory functions, the ECS represents an important therapeutic target to be elucidated. Cannabinoids, especially pCB or sCB, that manipulate the ECS as specific agonists or antagonists may potentially influence dysregulation. For this reason, more research is required to shed light on the complex interactions of the ECS in order to find new therapeutic tools for therapy of gynecological disorders and cancer.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflict of interests to declare.

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