Endometriosis

Excerpt from www.endometriosis.ca:

Endometriosis is a disease in which tissue similar to the lining inside the uterus (called “the endometrium”), is found outsidethe uterus, where it inducesa chronic inflammatory reaction that may result in scar tissue. It is primarily found on the pelvic peritoneum, ovaries, in the recto vaginal septum, on the bladder, and bowel. In very rare cases it has been found on the diaphragm and in the lungs[1,2].

Endometriosis affects an estimated 1 in 10 women during their reproductive years (ie. usually between the ages of15 to 49), which is approximately 176 million women in the world[3,4]. However, endometriosis can start as early as a girl’s first period and the menopause may not resolve the symptoms of endometriosis,especially if the woman has scar tissue or adhesions from the disease and/or surgery.

The symptoms of endometriosis include painful periods, painful ovulation, pain during or after sexual intercourse, abnormalbleeding, chronic pelvic pain, fatigue, and infertility,and can impact on general physical, mental, and social well being[1,5].

A general lack of awareness combined with a “normalisation” of symptoms results in a significant delay from when a woman first experiences symptoms until she eventually is diagnosed and treated[5].

There is no known cure and, although endometriosis can be treated effectively with drugs, most treatments are not suitable for longterm use due to sideeffects[1,3]. Surgery can be effective to remove endometriosis lesions and scar tissue, but success rates are dependent on the extent of disease and the surgeon’s skills. Pregnancy may relieve symptoms but is not a cure for the disease. Hysterectomy, with surgical removal of all the disease at the same time, may relieve symptoms, but is not a “definitive cure” either. Removal of the ovaries at the same time as a hysterectomy is performed increases the chances of pain relief but also results in an immediate menopause.

There is no known cause of endometriosis but it is highly likely that certain genes predispose women to develop the disease[6]. Thus, women have a higher risk of developing endometriosis if their mother and/or sister(s) are also affected[7].

It is also likely that environmental factors influence whether a woman is affected: for example, in a few papers it has been suggested that endometriosis is caused by exposure to dioxin (an environmental pollutant), although to date there is no proven link[8].

Pain. 2010 Dec;151(3):703-10. Epub 2010 Sep 15.

Endocannabinoid involvement in endometriosis.

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Abstract

Endometriosis is a disease common in women that is defined by abnormal extrauteral growths of uterine endometrial tissue and associated with severe pain. Partly because how the abnormal growths become associated with pain is poorly understood, the pain is difficult to alleviate without resorting to hormones or surgery, which often produce intolerable side effects or fail to help. Recent studies in a rat model and women showed that sensory and sympathetic nerve fibers sprout branches to innervate the abnormal growths. This situation, together with knowledge that the endocannabinoid system is involved in uterine function and dysfunction and that exogenous cannabinoids were once used to alleviate endometriosis-associated pain, suggests that the endocannabinoid system is involved in both endometriosis and its associated pain. Herein, using a rat model, we found that CB1 cannabinoid receptors are expressed on both the somata and fibers of both the sensory and sympathetic neurons that innervate endometriosis's abnormal growths. We further found that CB1 receptor agonists decrease, whereas CB1 receptor antagonists increase, endometriosis-associated hyperalgesia. Together these findings suggest that the endocannabinoid system contributes to mechanisms underlying both the peripheral innervation of the abnormal growths and the pain associated with endometriosis, thereby providing a novel approach for the development of badly-needed new treatments.

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Am J Pathol. 2010 Dec;177(6):2963-70. doi: 10.2353/ajpath.2010.100375. Epub 2010 Nov 5.

Antiproliferative effects of cannabinoid agonists on deep infiltrating endometriosis.

Leconte M, Nicco C, Ngô C, Arkwright S, Chéreau C, Guibourdenche J, Weill B, Chapron C, Dousset B, Batteux F.

Source

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Abstract

Deep infiltrating endometriosis (DIE) is characterized by chronic pain, hyperproliferation of endometriotic cells and fibrosis. Since cannabinoids are endowed with antiproliferative and antifibrotic properties, in addition to their psychogenic and analgesic effects, cannabinoid agonists have been evaluated in DIE both in vitro and in vivo. The in vitro effects of the cannabinoid agonist WIN 55212-2 were evaluated on primary endometriotic and endometrial stromal and epithelial cell lines extracted from patients with or without DIE. Cell proliferation was determined by thymidine incorporation and production of reactive oxygen species by spectrofluorometry. ERK and Akt pathways were studied by immunoblotting. Immunoblotting of α-smooth muscle actin was studied as evidence of myofibroblastic transformation. The in vivo effects of WIN 55212-2 were evaluated on Nude mice implanted with human deep infiltrating endometriotic nodules. The in vitro treatment of stromal endometriotic cells by WIN 55212-2 decreased cell proliferation, reactive oxygen species production, and α-smooth muscle actin expression. The decrease in cell proliferation induced by WIN 55212-2 was not associated with a decrease in ERK activation, but was associated with the inhibition of Akt activation. WIN 55212-2 abrogated the growth of endometriotic tissue implanted in Nude mice. Cannabinoid agonists exert anti-proliferative effects on stromal endometriotic cells linked to the inhibition of the Akt pathway. These beneficial effects of cannabinoid agonists on DIE have been confirmed in vivo.

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http://www.ncbi.nlm.nih.gov/pubmed/21057002

Fertil Steril. 2012 Oct;98(4):948-56.e1. doi: 10.1016/j.fertnstert.2012.06.009. Epub 2012 Jul 11.

Progesterone-dependent regulation of endometrial cannabinoid receptor type 1 (CB1-R) expression is disrupted in women with endometriosis and in isolated stromal cells exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).

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Source

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Abstract

OBJECTIVE:
To examine the differentiation-related expression of cannabinoid receptor type 1 (CB1-R) messenger RNA (mRNA) and protein in endometrial tissue obtained from women with and without endometriosis and to determine the impact of acute 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure on CB1-R gene expression in isolated endometrial stromal cells.

DESIGN:
Laboratory-based study.

SETTING:
University-affiliated medical center.

PATIENT(S):
Women with and without endometriosis undergoing volunteer endometrial biopsies after informed consent.

INTERVENTION(S):
None.

MAIN OUTCOME MEASURE(S):
Analysis of in vivo CB1-R mRNA and protein expression in human endometrial tissues and mRNA expression in isolated stromal cells after exposure to TCDD or a progesterone receptor antagonist (onapristone).

RESULT(S):
Expression of CB1-R mRNA and protein was highest during the progesterone-dominated secretory phase in control samples, but expression was minimal in the endometrial tissues acquired from women with endometriosis, regardless of the cycle phase. Although progesterone was found to induce CB1-R mRNA expression in endometrial stromal cells from control donors, steroid-induced expression of this gene was inhibited by cotreatment with either TCDD or onapristone.

CONCLUSION(S):
Our studies reveal a role for the anti-inflammatory actions of progesterone in regulating endometrial cannabinoid signaling, which is disrupted in women with endometriosis. We demonstrate for the first time that acute TCDD exposure disrupts cannabinoid signaling in the human endometrium.

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THE MOLECULAR CONNECTIONS BETWEEN THE CANNABINOID SYSTEM AND ENDOMETRIOSIS

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Abstract

The endocannabinoid system consists of an array of endogenously produced bioactive lipids that activate cannabinoid 1 (CB1) and 2 (CB2) receptors. Alterations of this system have been described in almost every category of disease. These changes can be protective or maladaptive, making the system an attractive therapeutic target. Little is known about the potential role of endocannabinoids in endometriosis development although this is a topic worthy of further investigation since endocannabinoid modulators have recently been shown to affect specific mechanisms critical to endometriosis establishment and maintenance. A literature review was herein performed with the aim of defining the regulation and function of the endocannabinoid signaling in in vitro and animal models of endometriosis. The components of the endocannabinoid system, CB1 and CB2 receptors and the enzymes NAPE-phospholipase D and fatty acid amide hydrolase are differentially regulated throughout the menstrual cycle in the endometrium and are expressed in deep endometriotic nodules and in sensory and sympathetic neurons innervating the lesions. Selective cannabinoid receptor agonists, such as WIN 55212-2, appear to have a favorable action in limiting cell proliferation and in controlling pain symptoms. Conversely, endometrial cell migration tends to be stimulated by receptor agonists. The phosphatidylinositol 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK)1/2 pathways either via receptor-dependent or independent effects seem to be involved in these processes. However, the underlying mechanisms of action are only just beginning to unfold. Given the complexity of the system, further studies are needed to clarify whether the endocannabinoid system might represent a promising target for endometriosis.

http://molehr.oxfordjournals.org/content/early/2012/08/24/molehr.gas037.short