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Review

Potential role of estrogen in maintaining the imbalanced sympathetic and sensory innervation in endometriosis

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ABSTRACT

Endometriosis, one of the most common benign gynecological diseases, affects millions of women of childbearing age. Endometriosis-associated pain is a major cause of disability and compromised quality of life in women. Neuropathic mechanisms are believed to play an important role. An imbalanced sympathetic and sensory innervation (reduced sympathetic innervation, with unchanged or increased sensory innervation in endometriotic lesions) has been demonstrated in endometriosis in recent studies. And it is believed to contribute to the pathogenesis of endometriosis-associated pain. It is primarily considered to be a natural adaptive program to endometriosis-associated inflammation. However, it is important to further clarify whether other potential modulating factors are involved in this dysregulation. It is generally accepted that endometriosis is an estrogen dependent disease. Higher estrogen biosynthesis and lower estrogen inactivation in endometriosis can lead to an excess of local estrogen in endometriotic lesions. In addition to its proliferative and anti-inflammatory actions, local estrogen in endometriosis also exerts potential neuromodulatory effects on the innervation in endometriosis. The aim of this review is to highlight the role of estrogen in mediating this imbalanced sympathetic and sensory innervation in endometriosis, through direct and indirect mechanisms on sympathetic and sensory nerves. Theoretical elaboration of the underlying mechanisms provides new insights in supporting the therapeutic role of estrogen in endometriosis-associated pain.

1. Introduction

Endometriosis is a chronic, benign, multifactorial gynecological disease affecting millions of women of childbearing age. It is estimated that endometriosis is present in 6–10% of reproductive age women (Khan et al., 2013) and in up to 20–40% of infertile women. Among women with pelvic pain, the prevalence goes up to 50% (Giudice, 2010). The various locations of endometriotic lesions make the patient suffer from diffuse, dull, but poorly localized feelings of pain, which are a major cause of disability and compromised quality of life in women and teenage girls (D'Hooghe and Hummelshoj, 2006).

Growing evidences tend to support the view that abnormal innervation of endometriosis plays a crucial role in the generation of pain (Mechsner et al., 2009; Anaf et al., 2000). There is a recently reported phenomenon in endometriosis that draws investigators' interest. Arnold et al. demonstrated an imbalance between sympathetic and sensory nerve fibers in peritoneal endometriosis (Arnold et al., 2012, 2013). The density of substance P positively stained sensory nerve fibers was significantly lower in the unaffected peritoneum compared to the endometriotic lesion, while the density of tyrosine hydroxylase (TH) positively stained sympathetic nerve fibers was significantly higher in the unaffected peritoneum in comparison to sympathetic nerve fiber density (NFD) in the lesion (Fig. 1). This imbalanced sympathetic and sensory innervation is consistent with the partial results demonstrated by Ferrero et al., in 2010 (Ferrero et al., 2010). Their research team found out that sympathetic nerve fibers were significantly lower in the mucosal and muscular layers near the endometriotic lesions compared with the area far from the lesions, while sensory NFD was not altered in the area near the endometriotic lesions. But this phenomenon has not been investigated in ovarian endometriosis and deep infiltrating endometriosis (DIE). This imbalanced innervation is believed to contribute to the pathogenesis of peripheral neuropathic pain in endometriosis. Therefore, it is important to

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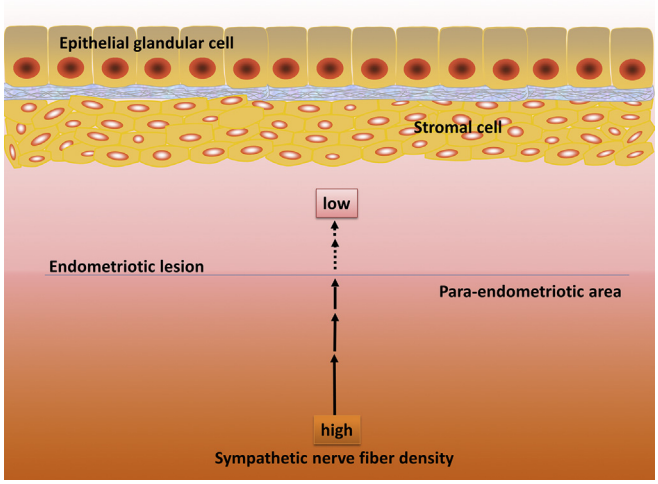

Fig. 1. Imbalanced sympathetic innervation in peritoneal endometriosis. Sympathetic nerve fiber density is significantly higher in the para-endometriotic area in comparison to that of the endometriotic lesion.

investigate the mechanism of this imbalanced innervation. Previous studies supposed that the imbalance between sympathetic and sensory nerve fibers in endometriosis was a natural adaptive program to endometriosis-associated inflammation (Arnold et al., 2012, 2013). However, further research is needed to help us have a better understanding of this imbalance.

Endometriosis is widely accepted to be an estrogen (E)-dependent disease. The dysregulation of the enzymes required to synthesize estrogen leads to the hyperestrogenism environment of endometriosis. More importantly, estrogen has been demonstrated to exert neuromodulatory effects through multiple processes (Wharton et al., 2012). The aim of this article is to highlight the potential role of estrogen in maintaining the imbalanced sympathetic and sensory innervation in endometriosis in detail, providing a new pathophysiologic vision of estrogen in endometriosis.

2. The role of estrogen and its receptors in endometriosis

A review performed by Huhtinen et al. summarizing the results of a series of studies indicates that all the enzymes required to synthesize estrogen are expressed in endometriotic lesions (Rizner, 2009; Attar and Bulun, 2006). The aberrant expression of these estrogen-metabolizing enzymes leads to higher E2 biosynthesis and lower E2 inactivation, and to an excess of local E2, which results in further proliferation of ectopic endometrium (Giudice and Kao, 2004). Increased production of local E2 induces prostaglandin E2 (PGE_2) formation and then stimulates cyclooxygenase type 2 (COX-2), which in turn stimulates the expression of aromatase, establishing a positive feedback cycle to enhance E2 production (Rizner, 2009).

There are two distinct isoforms of estrogen receptors (ERs): ERα and ERβ, the actions of which are regulated by ligand availability and by the presence of various coregulators (Musgrove and Sutherland, 2009). Estrogen stimulates the growth of endometrial cells mainly through the activation of ERα (Shang, 2006; Vivacqua et al., 2006). But many studies have shown that both ERs contribute to stimulation of the cell cycle and promotion of endometriotic stromal cells proliferation (Harris et al., 2005; Trukhacheva et al., 2009). Estrogens also exert anti-inflammatory functions by repressing several inflammatory genes including IL-8, IL-6, TNF-α. ERα and ERβ, mainly ERα, mediate the anti-inflammatory action of estrogens by inhibiting NF-κB activity and DNA binding, or by recruiting steroid receptor coactivator 2 (SRC-2) (Cvoro et al., 2008).

3. Potential role of estrogen in maintaining imbalanced sympathetic and sensory innervation in endometriosis

In addition to its proliferative and anti-inflammatory actions, are there any other pathophysiologic effects of estrogen on endometriosis? Here, the potential neuromodulatory effects of estrogen on the nervous system in endometriosis will be presented. Moreover, as far as we know, this is the first review that reveals the potential role of estrogen in maintaining imbalanced sympathetic and sensory innervation in endometriosis (Fig. 2).

3.1. Potential neuromodulatory effects of estrogen in endometriosis

Combined oral contraceptives (OCCs) are composed of estrogen (estradiol) and progestogen (progestin). It was reported that cyclic or continuous OCCs effectively reduced the baseline pain score for dysmenorrhea (Harada et al., 2008). Other reports showed that postoperative OCCs could also reduce the frequency and severity of recurrent dysmenorrhea compared with surgery alone (Seracchioli et al., 2009, 2010a, 2010b). Moreover, several studies showed that hormonal treatment significantly decreased the nerve fiber density in peritoneal endometriotic lesions, in comparison with lesions from women who did not receive hormone treatment (Tokushige et al., 2009). As a consequence, estrogen is believed to be involved in the modulation of endometriosis-associated pain as well as aberrant innervation in endometriosis.

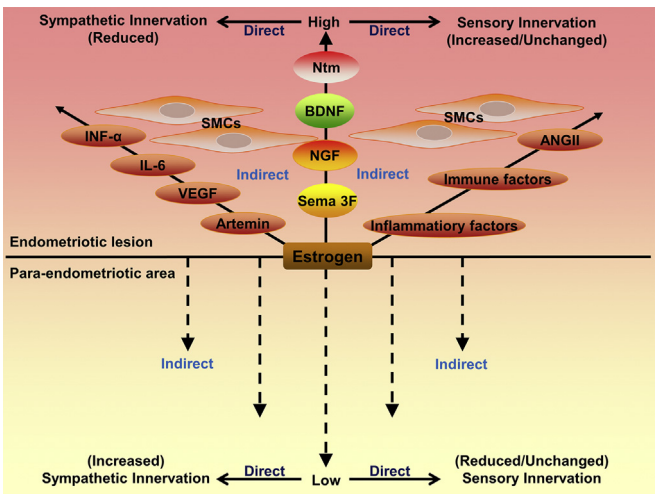

Fig. 2. Estrogen modulates the imbalanced sympathetic and sensory innervation in multifactorial mechanisms. High level of estrogen (top) acts directly on both sympathetic and sensory nerves in endometriotic lesion, partly leading to reduced sympathetic innervation and increased/unchanged sensory innervation. Estrogen also exerts up-regulation on specific molecules (such as Sema 3F, NGF, BDNF, Ntm, etc.) and induces degeneration of sympathetic nerves with preserved or increased sensory nerves. Moreover, SMCs, acting as a functional target, also respond to estrogen leading to a restricting environment for sympathetic nerve growth, but an permissive or a stabilizing environment for sensory nerve growth. In para-endometriotic area, opposite effects are induced by low level of estrogen (bottom). NGF: nerve growth factor; BDNF: brain derived neurotrophic factor; VEGF: vascular epithelial growth factor; Sema 3F: Semaphorin 3F; Ntm: neurotrimin; ANG II: Angiotensin II; SMCs: smooth muscle cells.

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