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Know Your Enemy: Potential Role of Cabergoline to Target Neoangiogenesis in Endometriosis

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Endometriosis is a chronic inflammatory gynecologic disease characterized by the presence and growth of endometrial-like tissue outside the uterine cavity, with an estimated prevalence of 10% in reproductive age women [1]. Symptoms are one of the main factors leading to suspect endometriosis and can severely compromise the quality of life. Endometriosis related symptoms, such as dysmenorrhea, chronic pelvic pain, dyspareunia, dysuria, dyschezia, and infertility, are not strongly related to the severity and stage of the disease, highlighting the complexity of underlying pathogenetic mechanisms and the heterogeneity of endometriosis presentation among affected women [2]. Although surgery and fertility treatments have a key role in the management of endometriosis and are effective in treating specific elements of the disease [2–4], they are not adequate for long-term management, and appropriate medical therapy is mandatory. Indeed, endometriosis has a high rate of recurrence after surgery, and appropriate second preventive therapy is currently recommended [2].

The therapeutic medical options are primarily based on the key role of estrogen and progesterone pathways in the maintenance and development of endometriotic implants [5]. The available hormonal therapies include estrogen-progestins, progestogens, anti-progestins, GnRH agonists, and aromatase inhibitors. Among them, hormonal contraceptives and progestogens are the most frequently prescribed for the management of endometriosis due to their efficacy and relative safety profile, as compared to GnRH agonists and aromatase inhibitors that are associated to significant side effects [2]. However, although the extensive clinical application of hormonal therapies, the evidence supporting their efficacy is still limited. Moreover, many women gain only partial or intermittent improvement of symptoms. In this scenario, the investigation and development of new therapeutic options are fundamental.

The growing body of evidence about the complex molecular pathways involved in the etiopathogenesis of endometriosis sheds new light on novel mechanisms and potential targets for drug design [5]. On that basis, the recent study by Karslioglu et al. [6] is of paramount importance to further highlight the potential role of cabergoline as a molecule able to interfere with the angiogenesis at the level of endometriotic implants.

The endometrial tissue is physiologically involved in the regulation of angiogenesis during the menstrual cycle, and available evidence suggests a dysregulation of these mechanisms in the eutopic endometrium of women with endometriosis [5]. Moreover, the ectopic endometrial cells after adhesion and degradation of extracellular matrix need to induce the neoangiogenesis in order to develop the endometriotic implants [5,7]. The neoangiogenesis is essential for the disease’s onset and progression, through different pathways: the increased levels of M2 macrophages as compared to M1 type [8]; the overall dysregulation of inflammatory response, favoring Th2 anti-inflammatory response; and the direct ability of endometrial stem progenitor cells to induce angiogenesis by the production of the vascular endothelial growth factor (VEGF) [5]. Available evidence showed a positive correlation between the VEGF peritoneal levels and the severity of the disease, with higher expression in active red lesions and deep infiltrating endometriosis [7]. Moreover, the key role of angiogenesis and VEGF binding its receptor type 2 (VEGFR-2) in the pathogenesis of endometriosis was further demonstrated by studies testing antiangiogenic agents, showing a reduction of lesion formation in both in vitro and in vivo models [5,7]. Nevertheless, many of these possible therapeutic options are associated with significant side effects that limit their application in the clinical practice.

In this scenario, cabergoline may represent a medication able to combine the antiangiogenetic effect with an adequate safety profile. Dopamine agonists are regularly used for the treatment of hyperprolactinemia and the inhibition of breastfeeding in the puerperium. Moreover, cabergoline is used for the prevention of ovarian hyperstimulation syndrome, where its action was related to the interference with the VEGF pathways by the dephosphorylation of VEGFR [7]. An effect of dopamine system on the VEGF pathways, and in general on angiogenesis, was further suggested by different pieces of evidence showing an induced
angiogenesis by the ablation of peripheral dopaminergic nerves in mice, enhanced angiogenesis in knockout mice for the dopamine receptor 2 (DR2), and in vitro studies suggesting that the activation of DR2 induces the internalization of VEGFR2 [9].

The direct effect of cabergoline on endometriosis implants through its effect on angiogenesis was demonstrated in a murine experimental endometriosis model: indeed, the exposure to cabergoline was associated with decreased number of active lesions, lower cellularity, and a significantly less developed vascularization [7]. Moreover, the presence of DR2 was demonstrated in both eutopic and ectopic endometrium, and its stimulation by cabergoline was associated to reduced phosphorylation of VEGFR2, to reduced gene and protein expression of VEGF, and to increased level of anti-angiogenetic markers [9].

All these pieces of evidence support the potential role of cabergoline for the management of endometriosis, which may represent a possible therapeutic option. Nevertheless, its therapeutic role needs to be further investigated, and the comparison with the other already available therapeutic options appears mandatory both to compare the efficacy and to test a possible synergistic action. Moreover, concerns regarding potential side effects, such as an increased incidence of cardiac valve insufficiency, may suggest the investigation of other non-ergotamine derived DR2 agonists [10], although the general safety profile and long clinical experience made cabergoline a drug of interest for further investigation.

Disclosure of interest

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper.

Authors’ contribution

All the authors conform the Journal and the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, contributed to the intellectual content of the study and gave approval for the final version of the article.