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Melatonin: The First Noninvasive Causal Therapy for Both Endometriosis and Adenomyosis?

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Abstract

Recently published data show that in vitro exposure of human normal and endometriotic endometrial epithelial cells to melatonin inhibits 17 β -estradiol-induced cell signaling pathways leading to their epithelial-mesenchymal transition, suggesting that melatonin might be used as a causative treatment agent for endometriosis. However, the same aberrant response of endometrial epithelial cells to 17 β -estradiol is intimately associated with the pathophysiology of adenomyosis, another challenging issue to both clinicians and researchers. The eventual *In vitro* effects of melatonin on epithelial-mesenchymal transition and the reverse process, mesenchymal-epithelial transition of adenomyotic cells obtained by biopsy, remain to be evaluated. Moreover, clinical research into the effects of melatonin in women suffering from endometriosis and adenomyosis, including dose-finding studies, should be encouraged.

Keywords: Endometriosis; Adenomyosis; Melatonin; Epithelial-mesenchymal transition; Mesenchymal-epithelial transition; 17 β -estradiol; Migration and invasion

Abbreviations: EMT: Epithelial-Mesenchymal Transition; TGF: Transforming Growth Factor

Introduction

It was shown recently that melatonin inhibits 17β-estradiol-induced migration, invasion and epithelial-mesenchymal transition in normal and endometriotic human endometrial epithelial cells [1]. These data suggest that melatonin may become the first noninvasive therapy which can be used to treat the very cause of endometriosis and not just to alleviate its symptoms. However, the beneficial effect of melatonin, in addition to endometriosis, can be expected exert similar effects in adenomyosis, another closely related pathology in which abnormally reactive endometrial epitelial cells are major players. In fact, the similarity of the respective pathophysiological mechanisms of endometriosis and adenomyosis [2] suggests that melatonin may also be useful to treat adenomyosis, another disease caused by aberrant behaviour of endometrial epithelial cells in response to 17β-estradiol. As for endometriosis, no noninvasive causal treatment for adenomyosis has not been made available so far.

Both endometriosis and adenomyosis are characterized by a profound alteration of cell signaling pathways, activated or silenced by 17β-estradiol, leading to epithelial-mesenchymal transition (EMT) of the endometrial epithelial cells. As a result of these alterations, the endometrium-derived cells acquire the ability to migrate to ectopic locations, to invade the adjacent tissues and to become resistent to apoptosis [3-4]. EMT is a physiological process, involved in normal functioning of the female reproductive organs, but its dysregulation can lead to pathological conditions, such as endometriosis, adenomyosis, and carcinogenesis [5].

The findings by Qi et al. [1] show that melatonin counteracts the estradiol-induced activation of the Notch pathway, which is a key signaling pathway not only in EMT but also in the reverse process, referred to as mesenchymal-epithelial transition (MET). The latter is associated with a loss of cell migratory freedom, restriction of invasiveness and cancer regression [6]. The finding that, in addition to estradiol-induced EMT, melatonin abolishes EMT induced by transforming growth factor (TGF)- b1 [1] suggests that melatonin may also be effective against cancer. Interestingly, melatonin has recently been shown to suppress fibrotic responses of a human mucoepidermoid cell line to TGF-b1 [7], suggesting that this drug may be involved in both EMT and MET regulations. These properties make melatonin an interesting candidate for both the prevention and treatment of endometriosis [1] and adenomyosis [8-10].

Conclusion

the study by Qi et al. [1] should encourage further *In vitro* studies evaluating the effects of melatonin on the EMT and MET processes in human cells obtained by biopsy of organs affected by different invasive pathologies, including adenomyosis and cancer.

Independently, the time appears ready for designing clinical dose-finding studies on *In vivo* effects of melatonin on endometriotic and adenomyotic cells from affected women.

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