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Social psychogenic stress promotes the development of endometriosis in mouse

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A B S T R A C T

Exposure to chronic stress *before* and well after the induction of endometriosis is reported to increase lesion sizes in rats, but it is unclear whether stress, exposed shortly *after* the induction of endometriosis, would also promote the development of endometriosis, nor is it clear what the underlying possible molecular mechanism is. This study was undertaken to test the hypothesis that chronic stress can promote the development of endometriosis. A prospective randomized mouse experiment was conducted that subjected mice with induced endometriosis to predator stress. In addition, a cross-sectional immunohistochemistry study was performed in ectopic and eutopic endometrial tissue samples from age- and roughly menstrual phase-matched women with ovarian endometriomas. It was found that the chronic psychogenic stress induced epigenetic changes in the hippocampus in mouse independent of endometriosis. It was also found that chronic psychogenic stress induced epigenetic changes in the hippocampus of mice with endometriosis, and seemingly activated the adrenergic signalling in ectopic endometrium, resulting in increased angiogenesis and accelerated growth of endometriotic lesions. Thus, chronic psychogenic stress promotes endometriosis development, raising the possibility that the use of anti-depressants in cases of prolonged and intense stress might forestall the negative impact of stress on the development of endometriosis.

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Introduction

Endometriosis, characterized by the deposition and growth of functional endometrial-like tissues outside the uterine cavity, is an oestrogen-dependent disorder affecting 6 – 10% of women of reproductive age (Giudice and Kao, 2004). It is a major contributor to pelvic pain and subfertility and a leading cause of gynaecological hospitalization in the USA (Eskenazi and Warner, 1997) and likely in many other countries in the world as well. Despite exponential growth in the number of publications on endometriosis in the last four decades (Guo, 2014), the exact pathogenesis still remains poorly understood (Garry, 2004) and few modifiable risk factors have been identified (Vigano et al., 2004).

Extensive epidemiological studies have shown that endometriosis impacts negatively on women's quality of life, work productivity, sexual relationship and self-esteem, mainly because of chronic, incapacitating pain and infertility (Culley et al., 2013; Denny and Mann, 2007; Fourquet et al., 2011; Lovkvist et al., 2016; Nnoaham et al, 2011). As a result, women with endometriosis are reported to have higher levels of psychological stress, depression and anxiety (Barnack and Chrisler, 2007; Eriksen et al., 2008; Low et al., 1993; Petrelluzzi et al., 2008; Quinones et al., 2015; Sepulcri Rde and do Amaral, 2009). Women with deep endometriosis-related pain are reported to have the highest levels of perceived stress, which are significantly reduced after surgical treatment (Lazzeri et al., 2015). Since endometriosis-associated pain is often intense, typically chronic and uncertain or uncontrollable (Denny, 2009; Lemaire, 2004) and occurs exclusively in females, the resultant psychological stress has nearly all the ingredients for exerting a potent negative effect on women with endometriosis (Karatsoreos and McEwen, 2013).

Stress is one of the most ubiquitous and well-studied environmental influences on health and disease in humans (McEwen, 2008). Chronic stress can alter immunological, neurochemical and endocrinological functions (Gunnar and Quevedo, 2007), and has been shown to promote tumour growth and metastasis (Nagaraja et al., 2016; Thaker et al., 2006). However, its role in the development of endometriosis has received scant attention.

Using a rat model of endometriosis, Cuevas et al. (Cuevas et al., 2012) reported that the exposure to stress *prior* to the induction of endometriosis increased both the number and severity of vesicles in rats. In addition, stress also increased infiltration of neutrophils in the colons and colonic motility (Cuevas et al., 2012). Thus, they concluded that stress 'may contribute to the development and severity of endometriosis . . . through mechanisms involving cell recruitment (e.g. mast cells), release of inflammatory mediators and deregulation of hypothalamic–pituitary axis responses in the hippocampus' (Cuevas et al., 2012). Their recent study also showed that exposure to uncontrollable stress 2 weeks *after* the induction of endometriosis displayed more anxiety in rats and had larger lesion size than those exposed to controllable stress or none (Appleyard et al., 2015).

While the study of Cuevas et al. (Cuevas et al., 2012) is the first that provides evidence for a link between stress and the development of endometriosis, there are still many stones left unturned. First, the stress protocol used in both Cuevas et al. (2012) and Appleyard et al. (2015) is swimming stress. While this protocol did induce psychological stress as shown by increased faecal pellet count in stressed animals, it also induced *physical* stress since a cumulative 10 min of swimming could be physically strenuous for an untrained mouse. It is unclear what effect on endometriosis there would be if a pure *psychological* stress is administrated. Second, the stress protocol started *before* the induction of endometriosis in Cuevas et al. (2012), or 2 weeks after the induction (Appleyard et al., 2015), in which endometriotic lesions are fully established. It is unclear as to whether stress, exposed shortly *after* the induction of endometriosis, would also promote the development of endometriosis. Third, while increased numbers and severity of vesicles in stressed rats were reported (Cuevas et al., 2012), it is unclear what the underlying possible molecular mechanism is. Lastly, while the study stated that the deregulated hypothalamic-pituitary-adrenal (HPA) axis may be responsible for stress-induced endometriosis promotion by showing reduced but statistically not significant serum corticosterone concentrations in stressed as compared with non-stressed rats and also decreased central corticotrophin-releasing factor (CRF) in the CA3 sub-region of the hippocampus independent of stress status, the evidence is far from air-tight. It is unclear how the deregulated HPA axis impacts on the development of endometriosis or through which signalling pathway(s). In addition, since the brain is known to undergo structural and even epigenetic changes under chronic stress (Hunter et al., 2015), better markers for chronic stress are available (Hunter et al., 2009, 2015).

In light of our recent finding that surgical stress accelerates the development of endometriosis through the activation of the adrenergic signalling pathway (Long et al., 2016a, 2016b), we postulated that chronic psychological stress may activate the adrenergic signalling pathway, in particular the adrenergic receptor 2 (ADRB2), increases angiogenesis, induces platelet aggregation and accelerates the growth of endometriotic lesions in mouse. Indeed, ADRB2 has been shown to be responsible for stress-induced promotion of tumour development (Thaker et al., 2006) and metastasis (Nagaraja et al., 2016) and also for the stress-induced acceleration of endometriosis development (Long et al., 2016a, 2016b).

This study was undertaken to test this hypothesis using a pure psychological stress protocol. In addition, hippocampal epigenetic markers of stress were used to validate the stress protocol since hippocampus, prefrontal cortex and amygdale are three regions in the brain that are known to be most sensitive to stress (Hunter et al., 2015). Since ADRB2 is indeed involved in stress-induced promotion of endometriosis development in mouse (Long et al., 2016a, 2016b), this study also shows that ADRB2 is expressed and may be functional in human ovarian endometriomas.

Materials and methods

Ethical approval

This study was approved in March 2013 by the institutional ethics review board of Shanghai OB/GYN Hospital, Fudan University. Efforts were made to conform to the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network's guidelines (http://www.equator-network.org/) in study design and execution.

Animals

Forty-two virgin female C57BL/6 mice, of 7 – 8 weeks old, were purchased from Shanghai BiKai Laboratory Animal Centre (Shanghai, China). They were maintained under controlled conditions with a light/dark cycle of 12/12 h and had access to food and water *ad libitum*.

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