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Unveil the pain of endometriosis: from the perspective of the nervous system

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Review

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Abstract

Endometriosis is a chronic inflammatory disease with pelvic pain and uncharacteristic accompanying symptoms. Endometriosis-associated pain often persists despite treatment of the disease, thus it brings a deleterious impact on their personal lives as well as imposing a substantial economic burden on them. At present, mechanisms underlie endometriosis-associated pain including inflammatory reaction, injury, aberrant blood vessels and the morphological and functional anomaly of the peripheral and central nervous systems. The nerve endings are influenced by the physical and chemical factors surrounding the lesion, via afferent nerve to the posterior root of the spinal nerve, then to the specific cerebral cortex involved in nociception. However, our understanding of the aetiology and mechanism of this complex pain process caused by endometriosis remains incomplete. Identifying the pathogenesis of endometriosis is crucial to disease management, offering proper treatment, and helping patients to seek novel targets for the maintenance and contributors of chronic pain. The main aim of this review is to focus on every possible mechanism of pain related to endometriosis in both peripheral and central nervous systems, and to present related mechanisms of action from the interaction between peripheral lesions and nerves to the changes in transmission of pain, resulting in hyperalgesia and the corresponding alterations in cerebral cortex and brain metabolism.

Introduction

Endometriosis is a debilitating and chronic gynaecological illness defined by the existence of endometrial-like tissue beyond the uterus and exhibits similar hormonal responses (Ref. 1). The prevalence rate in the population cannot be known precisely, but about 10% of women in their reproductive years have endometriosis (Ref. 2). Unfortunately, because an unequivocal clinical diagnosis is limited by individual differences, physician experience, the lack of specificity and non-invasive biomarkers, currently the delay in the diagnosis of endometriosis is inevitable (Ref. 3). Endometriosis is related to a range of symptoms, the most common of which are subfertility and chronic pelvic pain (CPP) (Ref. 4), the latter must be taken seriously as it has a massive effect on the patient's daily life and works as well as bringing a substantial financial burden (Ref. 5).

Although extensive and in-depth research put forward many hypotheses such as Sampson's implantation theory to explain its origin and pathogenesis, the exact aetiology remains elusive and controversial and the mechanism of pain associated with endometriosis is complex and still being investigated (Ref. 6). Although the pathogenesis of endometriosis is not entirely appreciated, several risk factors including anatomical abnormality, endocrine, hereditary, oxidative stress, immunological factors and inflammation are all contributors to the initiation and progress of endometriosis (Ref. 7). The new ESHRE guidelines recommended hormonal therapy or surgery for the treatment of pain symptoms associated with endometriosis (Ref. 8). However, they are not currently selected based on pain mechanisms (Ref. 8).

Unfortunately, endometriosis tends to persist even after excising or ablating all visible lesions. Besides, the stage of endometriosis has a poor correlation between the degree of subjective pain and the location, amount, size and severity of endometriotic lesions (Ref. 9). Endometriosis-related CPP may result from neo-neurogenesis, inflammatory pain, neuropathic pain, altered pain pathways, peripheral and central sensitisation and alterations in different brain regions (Refs 4, 10, 11). Given that the current summary of pain mechanisms related to endometriosis remains sparse at the cellular and molecular levels, we attempt to explore its possible mechanisms in the peripheral and central nervous systems (CNS) and demonstrate brain changes in imaging and biochemistry thus providing a possible theoretical basis for future clinical treatment (Table 1; Figure 1).

Neurogenesis and endometriosis

Previous studies have revealed changes in the nervous system in endometriosis. In patients with endometriosis, nerve fibre density in the endometriotic lesion was 14 times higher than control (Ref. 13). Deeply infiltrating endometriosis (DIE) showed elevated nerve density and expression of growth-associated proteins such as pan-neurotrophin receptors (NGFRp75)

Table 1. Definitions of relevant terms in this review

Term	Definition
Pain[a]	'An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.
Nociceptor[a]	'A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli'.
Central sensitisation[a]	'Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input'.
Peripheral sensitisation[a]	'Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields'.
Neuropathic pain[a]	'Pain caused by a lesion or disease of the somatosensory nervous system'.
Nociceptive pain[a]	'Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors'.
Inflammatory pain (Ref. 12)	'Inflammatory pain is the most important clinical symptom of inflammatory diseases. It is primarily caused by the sensitisation of primary sensory neurons (PSN) that are triggered by directly acting hyperalgesic mediators such as prostaglandins (PGE2) and sympathetic amines'.

[a]Definitions of these terms are from the 2020 International Association for the Study of Pain (IASP).

and nerve growth factor (NGF) (Ref. 14). Even with minimal to mild endometriosis, the endometrium of individuals is predominantly innervated by substance P and calcitonin gene-related peptide (CGRP)-positive nerve fibres, cholinergic and adrenergic nerve fibres (Ref. 15). In endometrial biopsies performed on patients, researchers also identified more neuroendocrine cells than those from the control group (Ref. 16). These small nerve fibres such as unmyelinated afferent C-fibres can transmit pain signals and modulate some functions of the autonomic nervous system (Ref. 17). The perineural invasion (PNI) (+) group, which had a higher nerve density, had higher visual analogue scale ratings for dysmenorrhoea, dyspareunia and chronic pelvic discomfort than the PNI (−) group (Ref. 18). However, the nerve density and pain scores were only relevant as the causal link was not reported yet. In recent animal models, unlike previous findings (Ref. 19), immunodeficient mice implanted with endometriotic lesions showed chronic pain behaviour but no significant difference in nerve density (Ref. 20). This also suggests that the mechanisms of pain associated with endometriosis are involved in an abnormality in the pain pathways with complicated pathogenesis.

The distribution of nerve fibres differs between normal human endometrium and endometriosis. Small nerve fibres were present in the functional layer of the endometrium in endometriosis patients, but similar innervation was not observed in healthy women (Ref. 21). However, some researchers had countered that small nerve fibres are not unique to patients with endometriosis. It was not rigorous to use nerve fibres as a diagnosis (Ref. 22). It was suspected that the altered innervation of the functional endometrial layer may be caused by the together influence of other diseases rather than the effects of endometriosis alone (Ref. 23). In addition, the distribution of nerve fibres within the endometriosis lesion was heterogeneous. In a cross-sectional study, by utilising a set of neuronal markers in samples from rectosigmoid endometriosis lesions, people detected larger nerve fibre densities at the edges of the nodules than at the centre (Ref. 24).

Endometriosis not only caused a change in the number and distribution of nerve fibres but also caused the nerve fibre types to change. Semaphorin, which was released by macrophages or activated fibroblasts in inflamed tissue in endometriosis patients, can induce degeneration of sympathetic nerves and necrosis, thus leading to the imbalance of the autonomic nervous system (Ref. 25). In vitro experimental models, peritoneal fluid from patients with endometriosis can induce an increased amount of germinated sensory neurites in the dorsal root ganglion and the decrease of sympathetic ganglion neurites (Ref. 26). An additional characteristic of endometriosis is that it is steroid-dependent with a complex hormonal imbalance (Ref. 27). In preclinical studies, it was found that high 17β-oestradiol could alter the distribution and/or numbers of nerve fibres containing vesicular acetylocholine transporter (VAChT), nitric oxide synthase (nNOS) and vasoactive intestinal polypeptide (VIP) (Ref. 28). This finding was supported by animal models. Both sympathetic and sensory nerve fibre markers were overexpressed at the site of induced endometriosis in mice. The increase in neurotrophic factors may be responsible for stimulating nerve development and boosting the growth of sensory nerves (Ref. 29). Further research into the specific mechanisms, NGFs in rats' ovaries were found to affect the expression of neurotransmitter-related enzymes in noradrenergic and cholinergic systems, causing the corresponding neurotransmitter content to change and subsequent cascade response (Ref. 30).

Moreover, endometriosis lesions can also modify pain by affecting the activity of nerve fibres. People unearthed that patients with endometriosis had lower vagus nerve activity (Ref. 31). Chronic pain often results from a depletion of the sympathetic nervous system (Ref. 32), and endometriosis also causes CPP. Although its mechanism is unclear, it encourages researchers to study the links between nerve change, inflammation and immune dysfunction (Refs 25, 33).

Nerves and neovessels

Experimental studies have shown that ectopic endometrial debris acquires neurovascular supplies through a series of complex mechanisms, and it then survives and develops (Ref. 34). In an attempt to treat pain, the patient with severe endometriosis received bevacizumab (Avastin®), a monoclonal antibody, resulting in the cessation of persistent dysmenorrhoea (Ref. 35). In the process of angiogenesis, the vascular epithelial growth factor (VEGF) has a powerful biochemical influence including its well-known effects on neovascularisation and angiogenesis (Ref. 36). The concentrations of macrophage migration inhibitory factor (MMIF), hypoxia-inducible factor-1a (HIF-1a) and VEGF were found to be higher in serum and endometrial tissue of endometriosis (EM) patients than in healthy women (Ref. 37). Among them, HIF may play a key role in maintaining the normal endometrial function, specifically in the expression of cellular and angiogenesis genes during progesterone withdrawal via the prostaglandin (PG) pathway during hypoxia (Ref. 38). Stimulation of endometriotic cells or the significantly upregulated transforming growth factor-β (TGF-β) expressions in patients' peritoneal fluid can also upregulate VEGF levels by promoting the activation of a series of VEGF-related signalling molecules such as cyclooxygenase-2 (COX-2) (Ref. 34) or blocking the DNA-binding protein 2 pathway (Ref. 39). However, in a case-control study, there was no significant difference in VEGF

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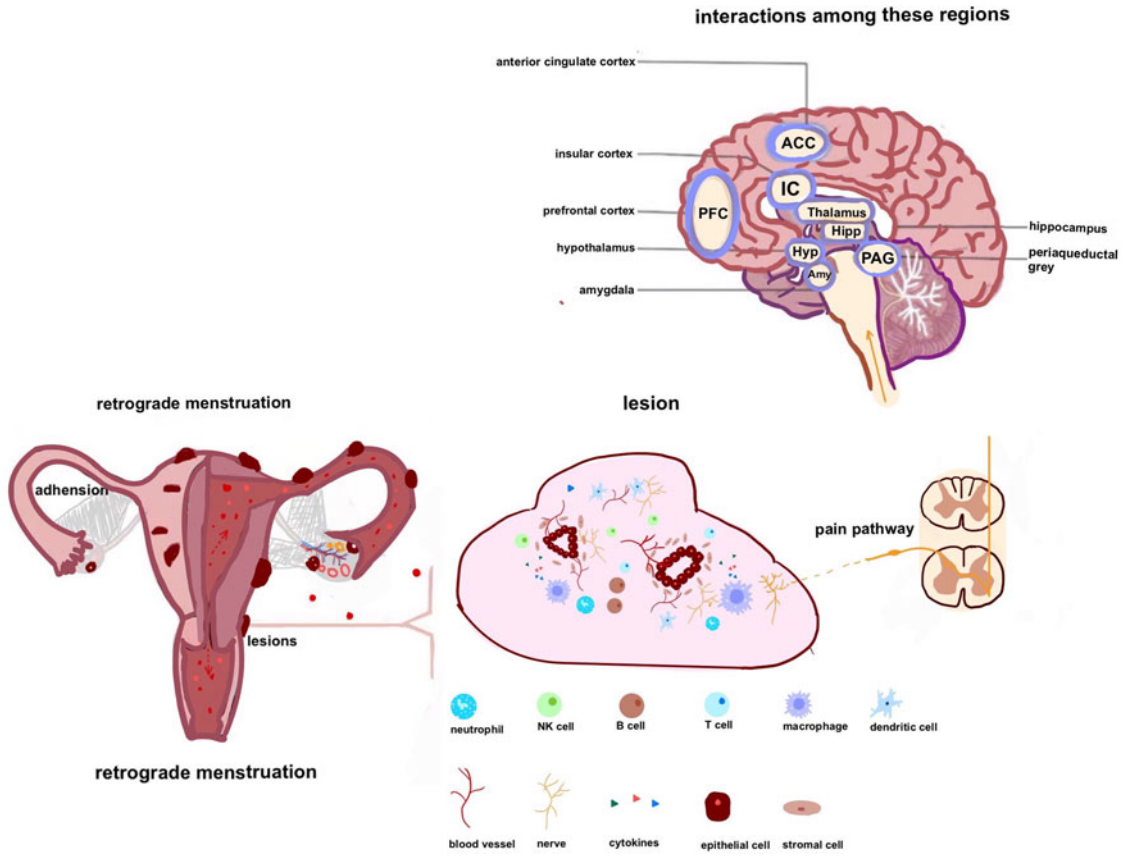

Fig. 1. Pain conduction pathway in endometriosis: endometrial debris can travel and infiltrate in several locations. In addition to stimulating neurogenesis and neovascularisation, it may release chemicals that attract diverse cells. The combination of these changes promotes microenvironmental changes around the lesion. Oxidative stress and inflammatory mediators can stimulate and sensitise pain-sensing nociceptors at primary afferent neurons in the area of the lesion. By modulating various ion channels, peripheral receptors result in increased sensitivity and hyperexcitability of nociceptor neurons (peripheral sensitisation). Inflammatory pain can progress into neuropathic pain as the disease state persists and progresses, causing neuronal damage. Pain processing may be altered by repetitive and persistent noxious stimulation, chronic inflammation and nerve injury, leading to central sensitisation. Besides, chronic pain is associated with alterations in the structure and function of the brain.

mRNA expression between patients with endometriosis and controls (Ref. 40). Based on clinical studies, it is possible that VEGF is particularly expressed in red endometriotic lesions and its expression correlates with the activity and the stage of endometriotic lesions (Ref. 34).

In fact, angiogenesis in endometriosis is a complex process in which multiple factors are involved (Ref. 41). Cells that have undergone drastic changes in the peritoneal fluid, such as macrophages, mast cells and other cells which are all involved in the regulation of angiogenesis (Ref. 42). Ectopic endometriotic lesions can also secrete chemokines that attract immune cells, whereas immune cells can secrete a variety of cytokines that influence the local microenvironment (Ref. 41). Within this microenvironment, the interleukin (IL) family is responsible for initiating inflammation as well as promoting angiogenesis by inducing the production of proangiogenic factors (Ref. 43). However, angiogenesis and its indirect influence on pain remain controversial. Patients with higher vascularisation in DIE lesions did not score higher on patient pain questionnaires (Ref. 44). But, the neovascularisation-based examination technique is effective for clearing hidden lesions and reducing postoperative pain recurrence (Ref. 45).

Sensitisation and inflammatory/neuropathic pain

Chronic pain can be broadly divided into three categories: nociceptive pain (which inflammatory pain is part of), neuropathic pain and nociplastic pain (Ref. 46). Inflammatory pain is caused by tissue injuries, which trigger inflammatory reactions (Ref. 47). Inflammation contributes to tissue pressure and dysfunction, and toxic substances around nociceptive receptors are responsible for neuropathic pain (Ref. 48). The International Association for the Study of Pain (IASP) defines neuropathic pain as pain caused by a lesion or disease of the somatosensory system. People with neuropathic pain may have peripheral and/or central sensitisation (Ref. 49). Clinical research of patients with endometriosis found that they suffer from complex pain, in which the neuropathic component also plays a role (Ref. 50). When a noxious stimulus acts on peripheral nociceptive neurons, they are activated to elicit action potentials. This nociceptive information follows sensory pathways into the CNS contributing to nociception (Refs 51, 52). Peripheral inflammatory insult stimulates peripheral nociceptors. Over time, the reducing ligand-gated ion channel thresholds, altered adhesion receptor expression and permeability indicate that these nociceptors are more sensitive to slight environment changes and more likely to respond to painful stimuli (Refs 10, 53).

Among patients with endometriosis, researchers find inflammatory cellular infiltrates such as IL-10, COX-2, VEGF and pain mediator prostaglandin E2 (PGE2) (Ref. 54). Additionally, the level of pro-inflammatory factors such as TGF-β1, IL-15 and IL-7 are correlated with dysmenorrhoea severity in endometriotic implants (Ref. 55). Through the TGF-β–Smad signalling pathway, high levels of TGF-β1 in the peritoneal fluid contribute to peritoneal endometriosis (Ref. 39). It is not clear whether the association is the result of endometriosis alone, further research is needed (Ref. 56). In other chronic inflammatory diseases,

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TGF-β1 injected into animal models inhibited CCL3/4 expression through the extracellular signal-regulated kinase (ERK) signalling pathway, reducing the inflammatory response and pain (Ref. 57). A pro-inflammatory cytokine, IL-1β, is overexpressed in endometriosis, which affects the neurotrophic factor, brain-derived neurotrophic factor (BDNF), through nuclear factor-κB (NF-κB) and Jun amino-terminal kinases (JNK) signalling pathways, exacerbating endometriosis-associated pain (Ref. 58). Additionally, endometriosis-induced vaginal hyperalgesia was positively correlated with nerve-innervating cysts and PGEs in peritoneal fluid, because peripheral nociceptors' tansient receptor potential vanilloid 1 (TRPV1) thresholds may be affected by PGE2 (Ref. 59). Although the expression of COX-2 (the rate-limiting enzyme synthesised by PGE2) was increased in peritoneal fluid in patients with endometriosis and it fluctuated with the menstrual cycle (Ref. 60). COX is implicated in neuroinflammation today, and excessive COX-2 expression can also contribute to neurodegeneration (Ref. 61). However, non-steroidal anti-inflammatory drugs, are weakly recommended in the current pain management guidelines (Ref. 8).

It is well established that oxidative stress is implicated in the pathogenesis of endometriosis. When reactive oxygen species and antioxidant levels are imbalanced, they can produce inflammatory mediators and growth factors (Ref. 62). Additionally, peritoneal protein oxidative stress markers were significantly associated with pelvic pain symptom scores in endometriosis (Ref. 63). Except for endometriosis lesions that secrete pain mediators, chemokines and cytokines, immune cells recruited by these substances also produce those abovementioned substances (Ref. 64).

A dysfunction of congenital or adaptive immune cells is a relevant mechanism for explaining endometriosis as well as its pain mechanisms (Ref. 65). The variations in the proportion of dendritic cells in endometriosis were not only linked to the abnormal immune response and inflammatory environment, but also to the pain sensitisation and generation of pain symptoms (Ref. 66). The stimulation of macrophages may result in the release of inflammatory mediators that attract circulating immune cells to inflammation sites, activate local immuneaccessory cells and affect peripheral nerve function (Ref. 67). The innervated peripheral nerve transduces noxious stimuli created by these inflammatory mediators into action potentials that propagate from the nerve to the spinal cord (Refs 68, 69). Sensory neurons recruited macrophages in a hormone-dependent way that subsequently supported the growth of the lesion and promoted axonal sprouting of sensory neurons further invading the surrounding tissue (Ref. 11). In addition, macrophage-derived insulin-like growth factor 1 (IGF-1) expression was increased in the mouse endometriosis model, and it may activate IGF-1R-mediated intracellular signalling pathways to promote pain hypersensitivity (Ref. 70). The bidirectional interactions between mast cells and the nervous system have also attracted attention. When mast cells degranulate, histamine can trigger the release of neuropeptides (Ref. 71), and peritoneal fluid from patients with endometriosis has higher levels of tryptase (a marker of degranulation) (Ref. 72). Reduced mast cell degranulation in endometriosis models has also been proven to reduce neurogenic inflammation and its resulting neurosensitisation (Ref. 73). C1q, mannose-binding lectin (MBL) and C1-INH concentrations are higher in the vicinity of endometrial lesions compared with the control group (Ref. 74). When C3 is blocked, it prevents the cascade of inflammatory signals in endometriosis (Ref. 75) and also affects mast cell degranulation in mice with EM (Ref. 76). Despite this, the method of modulating the immune system as an alternative therapy, such as using pentoxifylline, to treat endometriosis-associated pain remains ambiguous because there is insufficient evidence (Ref. 77).

Hormonal influences on endometriosis-associated pain

Endometriosis is an oestrogen-dependent gynaecological disorder (Ref. 78). Studies have shown that oestrogen regulates visceral pain by increasing neuronal activity or modulating neuronal plasticity (Ref. 79). The overexpression of steroidogenic factor-1, which participates in oestrogen biosynthesis, ultimately results in an overproduction of oestrogen (Ref. 80). The increase in local oestrogen biosynthesis could also be because of the up-regulation of aromatase expression induced by PGE2 (Ref. 81). Oestrogen can not only prolong induced hyperalgesia by regulating the autocrine mechanism activation at the plasma membrane but it is also related to neurogenesis and neurodegeneration by affecting proliferation or differentiation in neural stem/progenitor cells (Ref. 82). Researchers found in patients with endometriosis who received combined oral contraceptives that the amount of NGF and its receptors significantly decreased in the endometrium (Ref. 83). The oestrogen and NGF signalling pathways interact, and the oestrogen receptor (ER) – a receptor can promote NGF-induced neurogenesis and differentiation (Ref. 84). In peritoneal endometriotic lesions, slit guidance ligand 3, related to guiding axon growth, was regulated by ER agonists (Ref. 85). In addition, neuroimmune interactions modulated by oestrogen hormone signalling may contribute to the sensitisation of peripheral nerves (Ref. 11). It is still controversial how oestrogen may regulate pain since activation of ER-β reduces nociceptive sensation in rat visceral pain models (Ref. 86). A possible explanation is that oestrogen alters ERs in the spine, changing nociceptive sensation (Ref. 87). Experimental studies with endometriosis animals showed that inhibiting overactive protein kinase B (AKT) and ERK1/2 pathways reduced the pro-inflammatory microenvironment and aromatase P450 expression as well as E2 biosynthesis. It is a novel idea to suppress ER expression to prevent signal transduction in the future (Ref. 88).

Progesterone is one of the drugs used to treat endometriosis-related pain (Ref. 8). A possible mechanism for its pain relief is Sig-1R, which is a mediator of pain and can bind progesterone. As a consequence of progesterone use, nociceptor excitability is decreased by reducing TRPV1 expression on their membrane (Ref. 89). Chronic pain in endometriosis is also associated with dysregulated hypothalamic–pituitary–adrenal (HPA) axis function (Ref. 90). Studies of chronic pain associated with endometriosis have linked cortisol delta and adrenocorticotropic hormone delta to the severity of menstrual pain in white women (Ref. 91). It is important to note, however, that if cortisol levels are measured, the results may be reversed, depending on a variety of factors, including the location of the test and how stressed the crowd is (Ref. 90).

Other pain mechanisms

Endometriosis commonly causes anatomical distortions because of adhesions and fibrosis which can bring subfertility and persistent discomfort, as evidenced by considerable research (Ref. 92). Inside the fibrotic tissue of the lesion, new nerves were entrapped (Ref. 93), whereas there are also some rare conditions of endometriosis. Deep infiltrating endometriotic nodule entrapped the obturator nerve (Ref. 94). In a similar manner, sciatic endometriosis can also lead to sciatic nerve pain (Ref. 95) and may be involved in central pain sensitisation via the fractalkine/CX3CR1/P38-MAPK (mitogen-activated protein kinases) signalling pathway (Ref. 96). Compression of the sensory nerves that innervate the abdominal wall can also cause chronic pain, which may be one of the explanations for pain in abdominal wall endometriosis (Ref. 97). It should be noted that these are quite rare occurrences so is not broadly applicable to endometriosis-associated pain.

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In addition to endometriosis, postoperative adhesion has also been shown to be a contributing factor to CPP in several studies (Ref. 92). But an absolute conclusion that adhesions cause pain cannot be drawn. Further research is needed to demonstrate the complex nature of adhesions in CPP (Ref. 98). As most visceral organs seem particularly susceptible to mechanical distension, abnormal attachments may result in the increased stretch on internal organs causing persistent pelvic pain (Ref. 99). During the gradual enlargement of the cysts in patients with ovarian endometriosis, mechanical stimuli were detected by the nociceptors and mechanically sensitive cation channels opened, causing rapid depolarisation. The excited nociceptors carried information and sent noxious stimuli from the periphery to the spinal cord, resulting in pelvic deep discomfort and pain (Ref. 100). In addition, the faster fibrosis around the ovary reduced the normal tissue space, resulting in iron accumulation and oxidative stress, promoting the development of endometriosis and forming a vicious circle (Ref. 101).

Pain transmission in the spinal cord

The pain signal is then transmitted to the spinal cord dorsal horn and eventually to the CNS, where it is processed (Ref. 102). Different groups of projection neurons and interneurons are involved in this process to maintain excitatory and inhibitory functions, respectively (Ref. 103). Neurotransmitter glutamate is upregulated at the spinal level, resulting in enlargement of the pain field (Ref. 104), while dysuria and/or defecation may also occur, thus explaining how coexistent conditions may occur with endometriosis (Ref. 2). There was no surprise that patients with endometriosis experiencing CPP had myofascial dysfunction and sensitisation. When they adopt the relief posture, patients experience pelvic floor spasms caused by reactive contractions of the pelvic floor muscles (Ref. 105). Because of the complexity of the mechanism of visceral pain, the actual cause of discomfort between two adjacent organs, such as the bladder and uterus, is frequently misinterpreted and misdiagnosed (Ref. 5). Moreover, the interaction between autonomic innervation and visceral sensory neurons crossing the ganglion also contributes to neuroplasticity (Ref. 106).

Cell bodies of nociceptors, which innervate the viscera, reside in the dorsal root ganglion of the spinal cord (Ref. 107). It is thought that inflammation-related cytokines, chemokines and other factors modulate ion channel activity in postsynaptic neurons by binding receptors or activating second messengers (Ref. 108). Heat-sensitive TRPV1 receptors found on capsaicin-sensitive peptide sensory neurons exhibit allosteric regulation under the influence of inflammation or neurotrophic factors (Ref. 109). The amount of upregulation of TRPV1 and TRPA1 receptors was closely correlated with dysmenorrhoea and dyschezia severity in DIE nodules in the rectum and sigmoid colon (Ref. 110). Oxidative stress is one of the pathophysiological factors causing endometriosis. Free oxygen radicals that penetrate through TPRV1 in DRGs can cause neuropathy and injury (Ref. 111). Because of the decreased activity of the mitochondrial enzyme ALDH2, reactive aldehydes in women with endometriosis do not degrade in time, resulting in the buildup of reactive aldehydes. The presence of reactive aldehydes activates the TPRA1 channel and modified pain signals (Ref. 112). Alterations in the expression of ectonucleotidases that may metabolise released adenosine triphosphate (ATP) in endometriosis contribute to the accumulation of ATP in the microenvironment (Ref. 113). It has been suggested that persistent stimulation of peripheral fibres may result in the release of inflammatory neurotransmitters and neuromodulators, including ATP, which influences glial cells (Ref. 114). Studies have shown that ATP activates the capsaicin-sensitive TRPV1 channel via P2Y receptors in DRG neurons (Ref. 115). In endometriosis, the expression of ligand-gated ion channel purinergic receptor P2X3 is increased, resulting in repeated neuronal sensitisation and persistent pain (Ref. 116). According to one explanation, activation of the transcription factor 3 (ATF3)/activator protein-1 pathway increases the expression of P2X3 in the dorsal root ganglion (DRG), resulting in endometrioid-related hyperalgesia (Ref. 117). By selectively reducing or inhibiting P2X3 in the dorsal root ganglion, chronic pain was alleviated in rats, making it an effective method for modulating nociceptive signals and chronic pain (Ref. 118). The SCN11A (Nav1.9) was significantly higher in the peritoneum of women with CPP and endometriosis than in those with CPP alone (Refs 119, 120). In addition, acid-sensing ion channel activity was enhanced by PGE2 in DRG neurons, which resulted in acidosis-evoked pain, revealing a peripheral mechanism for PGE2 involvement in hyperalgesia (Ref. 121). Rodent models of endometriosis revealed abnormal activation of the NF-κB signalling in dorsal root neurons, resulting in the altered expression of ion channels such as TPRV1, TPRA1 and CGRP, causing chronic and spontaneous pain (Ref. 111). Despite studies exploring ion channels and endometriosis lesions, more research is needed to explain the relationship between its pain and ion channels or receptors in neurons (Ref. 122) (Figure 2).

Altered brain in endometriosis

There are connections between pain sensitisation and endometriosis in the CNS (Ref. 4). Neuroimaging and neurophysiological studies have found patients with chronic pain showed similar structural and functional changes in brain regions linked with pain cognition and emotional stability (Ref. 123). Even worse, detrimental structural alterations in the brain structure can lead to pain maintenance commonly known as hyperalgesia (Ref. 124). Secondary dysmenorrhoea is most often because of endometriosis. However between menstrual phases, several regions including caudate nucleus, hypothalamus and thalamus showed significant changes in grey matter (GM) volume in dysmenorrhoea subjects (Ref. 125). Further, in women suffering from dysmenorrhoea, brain metabolism was different and the entorhinal cortex appears to be involved in the patient's increased response to painful stimuli (Ref. 126). However, it is not clear whether those patients with dysmenorrhoea do have endometriosis.

Women with CPP had reduced GM volume in the thalamus, whereas women experiencing endometriosis-associated CPP showed decreases in more brain regions, such as the thalamus, cingulate gyrus, putamen and insula (Ref. 127). Endometriosis may result in altered endogenous pain modulation since the insula is one of the key regions of the descending pain inhibitory system (Ref. 128). The loss of neurons could be a logical explanation for a reduction in GM volume, but there is no evidence to support it (Ref. 129). Functional magnetic resonance imaging (fMRI) showed that when patients with pain-activated brain areas, cortical connections were enhanced (Ref. 130). Possibly because of the continued activation of the somatosensory pain system in patients with endometriosis, even during non-pain periods, the connectivity among the somatosensory cortex, dorsolateral prefrontal cortex, temporal cortex and orbitofrontal cortex was increased (Ref. 130). Comparing endometriosis-associated CPP patients with pain-free controls, greater interconnectivity between the insula and the medial prefrontal cortex (mPFC) was identified (Ref. 131). The mPFC may display diverse roles in pain. In addition to its role in modulating pain, mPFC also could lead to chronification of pain through its corticosteroid projection (Ref. 132). Functioning connectivity between the mPFC and periaqueductal grey (PAG) was negatively related to

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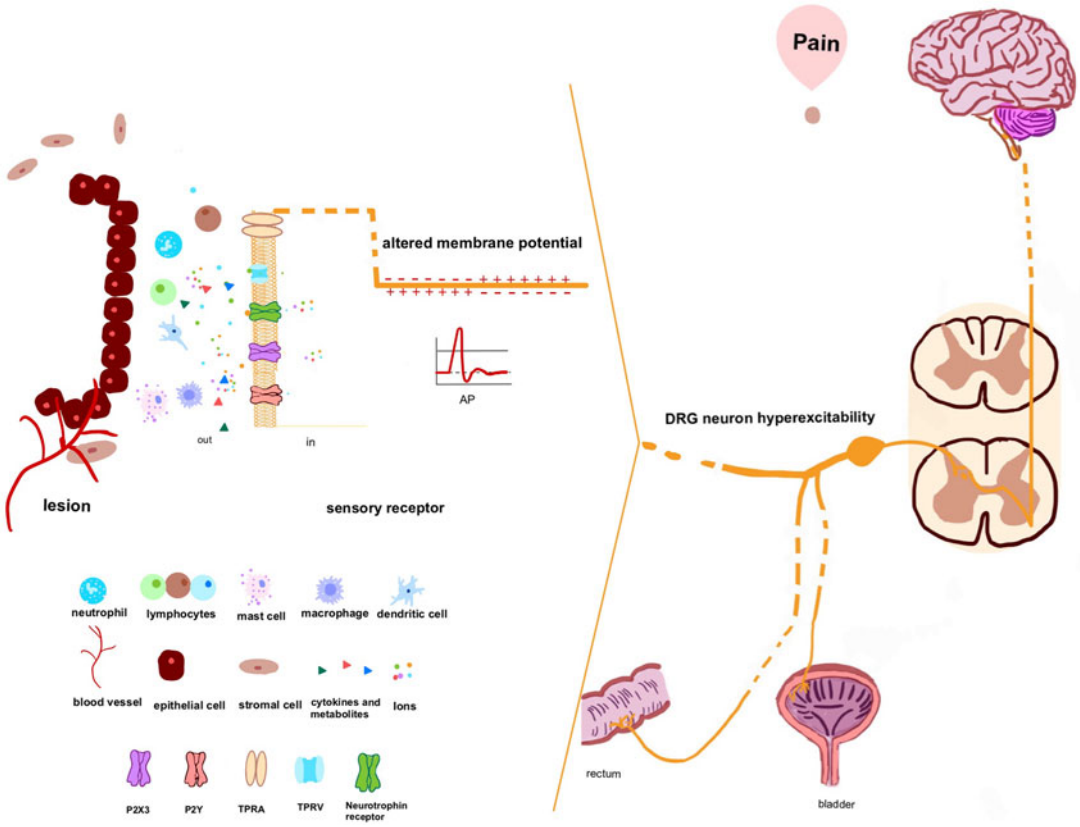

Fig. 2. Afferent fibre excitability is influenced by changes in the density, distribution and expression of a variety of ion channels. For example, inflammatory mediators cause primary sensory neurons to have a lowered threshold resulting in depolarisation and increased responsiveness to stimulus.

glutamate (known as a major excitatory neurotransmitter in the brain) concentration (Ref. 133). Compared with women with pain-free endometriosis, the CPP group showed an elevated concentration of combined glutamine–glutamate in the anterior insular (Ref. 131). The descending inhibition pathway plays a key role in regulating central pain transmission via PAG (Ref. 134). In the PAG, alterations in the expression of some receptors can affect the cross-talk between morphine receptor and *N*-methyl-D-aspartic acid receptor (NMDAR) thus affecting the analgesic signalling as well as individual pain response (Refs 135, 136). Some women with endometriosis suffer little or no pain despite the severity of disease, and this can be attributed to the larger volume of the PAG in their brain (Ref. 137).

When the abdomen of endometriosis macaques was activated below the standard pain threshold, abnormal activity of the thalamus and insular cortex was detected, indicating that these regions were responsible for the alteration of pain (Ref. 138). After being administered with dienogest and morphine respectively, activation of these regions, observed by fMRI, was decreased (Ref. 138). In general, exogenous opioids such as fentanyl are routinely used as strong analgesics, but because of the high risks of abrupt withdrawal and hyperalgesia, they are not recommended for chronic pain (Ref. 139). Prophylactic use of anti-NGF antibody mAb911 can, however, prevent the development of structural changes in the brain before they occur (Ref. 140). An endometriosis preclinical study has shown that COX-2 expression is elevated in spinal, thalamic and cortical areas, which are involved in processing pain in the CNS (Ref. 120). In turn, this results in excess PGE2 in the cerebrospinal fluid, where PGE2 has previously been found to function as a central pain sensitiser (Ref. 141). Rats with EM pain sensitisation had fewer neurons in the thalamus and left olfactory tubercle, suggesting the thalamus might be involved in central sensitisation (Ref. 142). Some patients with endometriosis also have chronic pelvic pain syndrome (CPPS). Although CPPS patients also experienced changes in brain structures such as the thalamus, anterior cingulate cortex (ACC) and PFC (Ref. 143).

The hippocampus has long been associated with cognitive functions but it is also involved in pain processing (Ref. 144). As shown by microarray analyses and confirmed by quantitative polymerase chain reaction, altered gene expression such as up-regulated Gpr88 and down-regulation of Nptx2 was found in several brain regions in endometriosis mice (Ref. 145). Connections between the hippocampus, thalamus, insula, striatum and cerebellum are increased in patients with endometriosis, and reductions in such connections when analgesic psychotherapy is used (Ref. 146). In the anterior segment of the hippocampus, the rAL region affects the HPA axis, which is associated with anxiety and pain (Ref. 146). However, studies have shown that the hypothalamic–pituitary–gonadal axis and HPA axis interact in women who suffer from dysmenorrhoea, so it is hard to pinpoint the exact mechanism (Ref. 147). TRPV1 and NMDAR, modulating neuroplasticity and synaptic excitability (Ref. 148) were strongly expressed in the ACC, thalamus and hippocampus of rats with endometriosis-associated pain (Ref. 149). The formation of an immune oxidative environment within the hippocampus of endometriosis rats is one of the mechanisms leading to pain sensitisation, whereas the elevated oxidative state in the hippocampus was correlated with a lower level of BDNF (Refs 150, 151). Astrocytes and microglia are thought to be responsible for many inflammatory processes in affected brains, including secretion of inflammatory mediators and stimulation of the innate immune system (Ref. 152). In addition, mast cell degranulation was increased in the hippocampal tissues of endometriosis rats (Ref. 151), whereas microglia and astrocytes are activated by mast cells, aggravating neuroinflammation (Ref. 153) (Figure 3).

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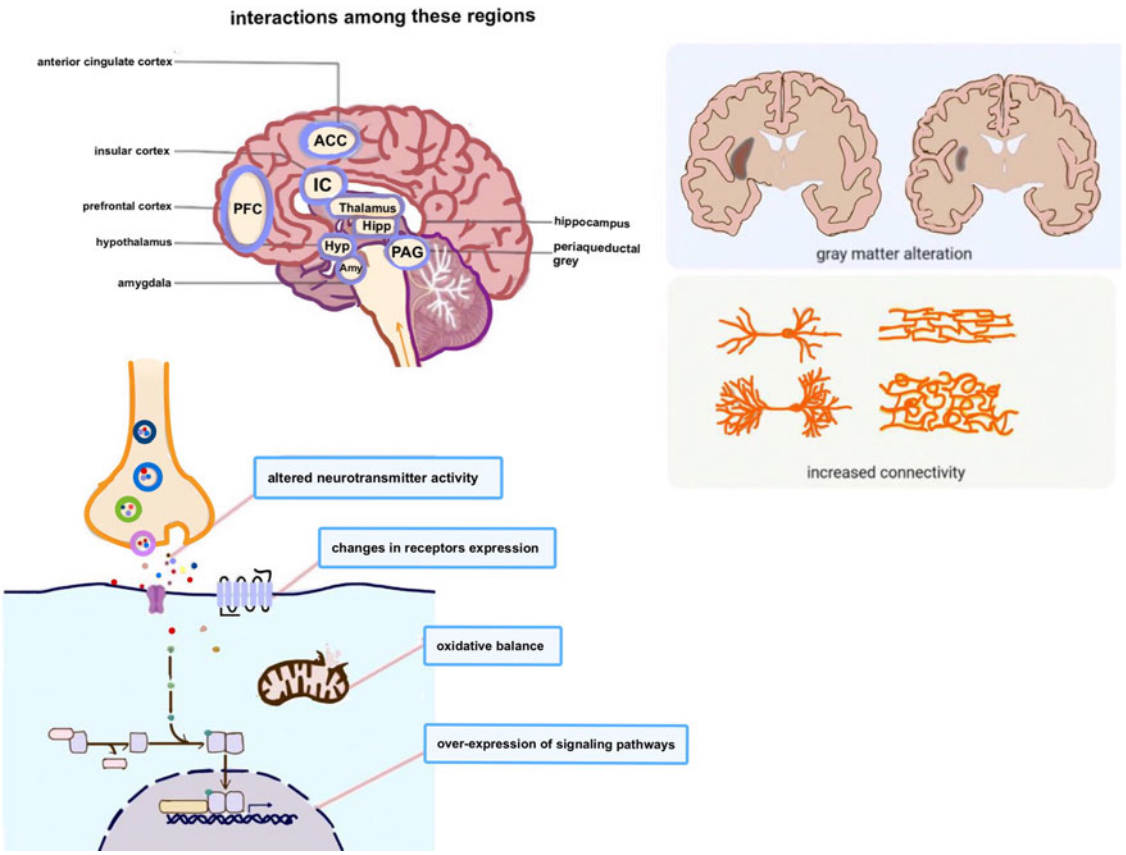

Fig. 3. Endometriosis-associated pain is linked to changes in brain structure and function, dysregulation of pain pathways and increased activity in brain regions. During the processing of pain information, multiple brain regions may interact with each other through several sophisticated mechanisms. Although complex and delicate interactions between distinct types of neurons in the specific regions have attracted high interest, the mechanisms underlying their mutual interactions are still not fully understood.

Conclusion

Pain in endometriosis is vital and complex, but few studies thoroughly outline the relationship between pain and the nervous system as well as brain metabolism. We summarise the most recent achievements in endometriosis-related pain in terms of neurogenesis, changes in pain transmission and peripheral and central sensitisation with corresponding changes in the cerebrum. As pain sensitisation in endometriosis is often overlooked in clinical practice, we hope that this review can inspire recognition of endometriosis-related pain and give more individualised treatment. In the future, with the wide utility of the multiparameter single-cell technique and the breakthroughs in neuroimaging, progress will be made in digging deeper into pain mechanisms in endometriosis, identifying new potential targets during the production and transmission of pain, developing novel pharmaceuticals precisely targeting the molecular mechanisms and enabling women to reduce the occurrence of chronic pain.

Search strategy and selection criteria

From October 2021 to June 2022, we searched databases on Medline, PubMed and Google using the key words 'chronic pain', 'endometriosis', 'endometriosis and brain', 'pathogenesis', 'ion channels', 'angiogenesis', 'pain', 'nerve fibre', 'sensitisation', 'oestrogen'. There were no restrictions on article types, date of publication or language. For this review, we prioritised the most recent and definitive original articles, large randomised trials, meta-analyses and international guidelines.

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Conflict of interest. The authors declare that they have no competing interests.

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