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# Endometriosis pain and acupuncture

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ABSTRACT

Endometriosis is a common cause of pain in the pelvic region in women. Endometriosis pain has often been considered to be a homogeneous condition. However, multiple mechanisms have been shown to contribute making it a therapeutic challenge. Many of the current medical treatments for it include oral drugs like non-steroid anti-inflammatory drugs, contraceptives, progestogens, androgenic agents, gonadotrophin releasing hormone analogues, as well as laparoscopic surgical excision of the endometriosis lesions. In many patients these treatments are insufficient or associated with side-effects. Three studies have described the application of different needle stimulation techniques (acupuncture) and the results suggest that acupuncture may be a valuable treatment option to some.



## 1. Introduction

Endometriosis is a multifactorial condition that can result in long-lasting visceral pelvic pain and infertility [24,35,76,77,12]. The condition is affecting approximately 10–15% of women in reproductive age [82].

The endometrial tissue is innervated by nerve fibres that may interact in the local oestrogen dependent inflammatory processes [74,7] leading to angiogenesis, adhesions, fibrosis, scarring [27] and ultimately in perceived pain [49].

Nociceptors are found in most visceral tissues including the uterus and cervix Tong et al. [85]. There is increasing evidence that endometriosis elicits changes in the population of uterine nociceptors. For example, women with endometriosis have many small unmyelinated nerve fibres in the functional layer of their endometrium. These nerve fibres are probably nociceptors, invading peritoneal endometriotic lesions [11], and are not present in women without endometriosis [71]. This suggests that there is abnormal sprouting of nociceptors in the endometrium and in peritoneal endometriotic lesions in women with endometriosis. Such nerve sprouting is likely caused by increased levels of NGF and GDNF [4,72].

Probably many of the nociceptors in the endometrium have the properties of 'silent nociceptors' [26]. These nociceptors are normally silent without responding to mechanical (pressure or distension) or thermal stimuli. When the surrounding tissue is inflamed however, they become sensitized i.e., change from being exclusively noxious stimulus detectors to detectors also of innocuous inputs [15]. This peripheral sensitization represents a form of stimulus evoked functional plasticity of the nociceptor. Sensitizing agents (PGE2, kinins, amines, growth factors, chemokines and cytokines) reduce the threshold level of activation and increase the responsiveness of the terminal by binding to specific receptors expressed on the membrane of the nociceptor terminal. [53,56,57,67]. The exact function and interrelationship of the different second messengers in nociceptor signalling remains to be established as it for the moment remains unclear what determines the use of the varying signalling pathways in nociceptive neurons especially as most of them are polymodal e.g., respond to multiple kinds of stimuli. Peripheral sensitization results in hyperalgesia i.e. increased sensitivity in the receptive field of the nociceptive neuron (primary hyperalgesia).

A common aspect of endometriosis pain is spontaneous pain (stimulus-independent pain). This pain may arise from signal molecules continuously released from the cysts that act on nociceptor peripheral terminals to either produce a depolarization sufficient to initiate action potentials or a reduction in threshold levels such that innocuous stimulus (as for example pulsation of blood vessels) now activate what had been high-threshold thermo- and mechanonociceptors. This spontaneous pain is transmitted in C-fibres.

### 1.1. Dorsal root ganglion

Exposure of naive neurons to inflammatory stimuli results in sensitization of the nerve i.e., hyperalgesia. This hyperalgesic

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state lasts for a few hours. However, even if the sensitivity partly decreases it remains increased for weeks i.e., in a primed state. Interestingly, hyperalgesia induced in the primed state is markedly prolonged as compared to the naive state. This could explain the the increased sensitivity seen between menses and also the long duration of the hyperalgesia during menses. The establishment as well as the maintenance of the primed state is PKCϵ-dependent. If in the primed neuron PKCϵ is blocked the neuron returns to the naive state [31].

As endometriosis progresses there is a risk that the peripheral axon of nociceptor afferents is damaged, due to extensive fibrosis and/or scar formation. If so marked changes in transcription may occur in the soma. Some of these represent attempts by the neuron to survive, others are attempts for the axon to re-grow, but many changes are maladaptive and produce alterations in function that can drive endometriosis (neuropathic component). For example there are alterations in the expression and distribution of sodium and potassium ion channels, increasing membrane excitability in the injured axon, so that ectopic impulses are generated without any peripheral stimulus Cummins and Rusk [86]. This ectopic excitability contributes to spontaneous pain. Ectopic firing may also originate from the DRG neurons. This firing may be attributed to neighbouring intact fibres in the DRG that have been exposed to cytokines such as tumour necrosis factor alfa (TNFα) produced by deafferented Schwann cells [84].

## 2. Transmission of pain signals in the dorsal horn of the spinal cord

### 2.1. Central terminal of nociceptors

In addition to regulating the flow of information by transmitter release, nociceptor neurons also produce chemokine signals after axonal injury that activate microglia in the dorsal horn to contribute to alterations in sensory processing in the spinal cord.

## 3. Structural reorganization

In patients where the endometrical change has resulted in a peripheral nerve injury, there is a new growth and/or sprouting of the central terminals of the low-threshold afferents into the zone of the dorsal horn that normally are exclusively occupied by the nociceptor terminals. Such a phenomenon could explain the intractability reported by some patients with endometriosis pain [22].

## 4. Central sensitization and activity dependent plasticity

Central sensitization begins with a cascade of events in the dorsal horn of the spinal cord and the glutamate-activated NMDA receptor. During central sensitization, this receptors responsiveness to glutamate is increased as is its distribution from intracellular stores to the synaptic membrane. The increase in excitability of the secondary neurons means activation by inputs that are normally subthreshold and increased response to suprathreshold input [84]. This change will clinically be manifested as a lowered threshold for eliciting pain where innocuous stimulation results in perceived pain, i.e., allodynia, and or an exaggerated or amplified response to noxious stimuli, i.e., hyperalgesia, and also the spread of sensitivity to non-injured areas known as *secondary hyperalgesia*.

Microglia likely plays a key role in the synthesis of cytokines and chemokines resulting in a widespread central induction of COX-2 contributing to the generalized aches and pains, loss of appetite, and changes in mood and sleep cycle that together constitute the sickness or illness syndrome, a feature of endometriosis.

These findings have important implications for therapy. First, COX-2 inhibitors must be targeted to central as well as peripherally induced COX-2. The central site of their action appears to be a major component of their analgesic activity. In addition, treatment aimed at reducing sensory inflow into the central nervous system, such as regional or epidural local anaesthesia during surgery, will not prevent the humoral-mediated central induction of COX-2 and may need to be supplemented by therapy with COX/COX-2 inhibitors [84].

## 5. Viscero–visceral reflexes

Vaginal hyperalgesia in endometriosis is reported to be due to estrogen-sensitized cysts Cason et al. [87]. Since the cysts are innervated by autonomic and sensory nerve fibres [11] This supply connects the implants directly with the central nervous system via the splanchnic and vagus nerves suggesting that the vaginal hyperalgesia involves viscero–visceral interactions [8]. Other supporting studies show that the activity in the sympathoadrenal axis and its modulation by vagal afferents can have a powerful impact on the pain and inflammatory response Schlereth and Birklein, [88].

## 6. From nociceptive projection neurons in the spinal cord to the brainstem, hypothalamus, thalamus and cortex

Projection neurons in the spinal cord transfer nociceptive input from the dorsal horn of the spinal cord to the brainstem, hypothalamus, and thalamus and then, through relay neurons, to the cortex Derbyshire [89]. Supraspinal, brain mechanisms are increasingly recognized as playing a major role in the representation and modulation of the pain experience Ren and Dubner [90]. Functional imaging and positron emission transmission scanning have shown that acute pain activates primary and secondary somatosensory (S1 and S2), insular (IC), anterior cingulated (ACC), and prefrontal cortices (PF) whereas chronic pain engages brain regions critical for cognitive and emotional assessments. Activation of these neural circuits may then contribute to inter-individual variations and disabilities associated with chronic pain conditions [6].

Human brain imaging has provided new insights into how different psychological states affect pain Scheedel et al. [91]. When subjects are distracted from pain there is an activation of periaqueductal grey (PAG), ACC, and PFC suggesting that these regions may be involved in the modulatory circuitry related to attention. Hypnotic suggestions also alter pain-evoked activity, but the specific regions involved depend on the nature of the suggestions. Interestingly, negative emotional states enhance pain-evoked activity in limbic regions. Also, the anticipation of pain can activate pain-related areas and cerebellum, even in the absence of a physical pain stimulus [10]. Cognitive modulation of pain by attention involves early sensory processing in S2–IC and later processing in ACC [80]. Attention modulation may in part reflect a change in cortical processing and in part a decrease in ascending afferent input from the spinal cord due to activation of descending noxious inhibitory controls. Understanding these modulator mechanisms is critical to the development of fully effective therapies for the treatment of endometriosis pain Dunckley et al. [92].

## 7. Disinhibition

Powerful tonic and phasic inhibitory events acting, pre-and postsynaptically, focus sensory input so that it produces a limited, appropriate, and brief response to any given input. Within the spinal cord, this is mediated by inhibitory neurons that release the inhibitory neurotransmitters' glycine and GABA. Descending