

Is there a role for acupuncture in endometriosis pain, or ‘endometrialgia’?

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Abstract

Endometriosis is a common cause of pelvic pain in women, many of whom suffer a progression of symptoms over their menstrual life. Symptoms may include combinations of abnormal visceral sensations and emotional distress. Endometriosis pain, or ‘endometrialgia’ often has a negative influence on the ability to work, on family relationships and sense of worth.

Endometrialgia is often considered to be a homogeneous sensory entity, mediated by a specialised high threshold sensory system, which extends from the periphery through the spinal cord, brain stem and thalamus to the cerebral cortex. However, multiple mechanisms have been detected in the nervous system responsible for the pain including peripheral sensitisation, phenotypic switches, central sensitisation, ectopic excitability, structural reorganisation, decreased inhibition and increased facilitation, all of which may contribute to the pain.

Although the causes of endometrialgia can differ (eg inflammatory, neuropathic and functional), they share some characteristics. Endometrialgia may be evoked by a low intensity, normally innocuous stimulus (allodynia), or it may be an exaggerated and prolonged response to a noxious stimulus (hyperalgesia). The pain may also be spontaneous in the absence of any apparent peripheral stimulus.

Oestrogens and prostaglandins probably play key modulatory roles in endometriosis and endometrialgia. Consequently many of the current medical treatments for the condition 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. However, management of pain in women with endometriosis is currently inadequate for many. Possibly acupuncture and cognitive therapy may be used as an adjunct.

Keywords

Acupuncture, endometrialgia, endometriosis, pain, pain treatment.

Introduction

Endometriosis was first described by Daniel Shroen in 1690 in *Disputatio Inauguralis Medica de Ulceribus Ulceri*, in which he depicted sores throughout the ‘stomach,’ bladder, intestines, and broad ligament which had a tendency to form adhesions that linked visceral areas together. Later, in 1769, Arthur Duff reported on the intense pain and suffering of these women, with morbid symptoms that manifestly change the disposition of the entire body.

Endometriosis occurs in approximately 10% of women of childbearing age and is defined by the

abnormal presence of endometrial tissue outside the uterus, usually in the abdominal/pelvic cavity.¹⁻³ These abnormal tissues are commonly referred to as ‘ectopic growths’, ‘lesions’ and ‘implants’. The pain symptoms usually originate in the reproductive organs but can also involve the urinary or intestinal tracts if endometriosis implantation has occurred there. The presentation and physical appearance of endometriosis is very variable and can be characterised by a chronic intraperitoneal inflammatory process and adhesions. The diagnosis is made by tissue biopsy identifying endometrial glands and stroma outside the uterus.⁴⁻⁶

Identification of possible mechanisms in pelvic pains, like endometriosis, has contributed to a major advance in our understanding. Future steps require the development of diagnostic tools that will allow us to identify the mechanisms of pain in an individual patient and the therapies (drugs, sensory stimulation techniques, cognitive behavioural techniques) that act specifically on these mechanisms. This strategy will allow us to take a rational rather than an empirical trial and error approach to the treatment of endometrialgia. In the present review we present some mechanisms of chronic pain that may have implications for endometriosis pain and its treatment.

These ectopic endometrial implants may initiate an inflammatory response by activating glial cells and by recruiting immune cells and macrophages.⁷⁻⁹ These cells produce cytokines and chemokines that induce an increased expression of cyclooxygenase (COX)-2.¹⁰ Expression of COX-2 leads to increased production and accumulation of prostanoids, especially prostaglandin E2 (PGE2). Elevated PGE2 induces abnormal expression of steroidogenic

proteins, leading to increased biosynthesis of oestrogens. Autonomous production of oestrogens induces an upregulation and synthesis of several growth factors which may serve as autocrine and paracrine factors to stimulate cell proliferation, angiogenesis and nerve sprouting (Fig 1).¹¹⁻¹⁶

Simultaneously, PGE2 exerts a direct action on endometriosis and endothelial cell proliferation. PGE2 and nerve growth factor (NGF) also exert direct and indirect actions on the sensory nerve terminals in the endometriotic tissues resulting in pelvic pains.^{17,18} The most common of the pelvic pains is dysmenorrhoea. Other pains include dyspareunia, obstipation and chronic abdominal and/or low back pain.^{19,20} Although endometrialgia is essentially a sensation, it has, like all types of pain, cognitive and emotional components.²¹ When comparing women with pelvic pain, with and without endometriosis, it was found that the symptoms in women diagnosed with endometriosis were associated with a higher degree of signs of psychoticism, introversion and anxiety.^{21,22} However, recently Eriksen and coworkers found no significant

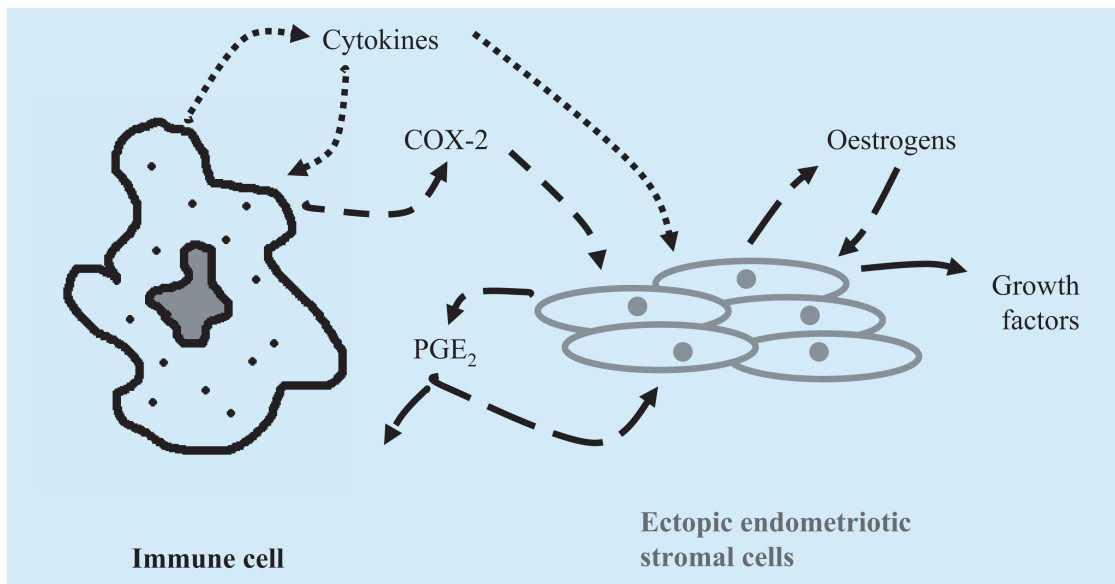


Figure 1 This shows a hypothetical model of endometriosis. Endometrial tissue enters the peritoneal cavity, in a retrograde direction. The tissues initiate an inflammatory response by recruiting immune cells and macrophages and by activating glial cells. These cells produce cytokines and chemokines that induce overexpression of cyclooxygenase (COX)-2 in macrophages and ectopic endometriosis tissues as well as in the nervous system. Expression of COX-2 leads to increased production and accumulation of prostaglandin E2 (PGE2). Elevated PGE2 induces aberrant expression of steroidogenic proteins in the ectopic endometriosis stromal cells, leading to abnormal biosynthesis of oestrogens. Autonomous production of oestrogens by ectopic tissues induces the expression of growth factors, which serve as autocrine and paracrine factors to stimulate cell proliferation and angiogenesis. Modified from Wu and collaborators.¹³³

differences between women with endometriosis,²³ with or without pain, in depression or anxiety and no associations between pain severity and depression or anxiety. They concluded that coping strategies appear to be of major importance to the psychological consequences of endometriosis.

It has been suggested that some women with endometriosis and pelvic pain may suffer from autoimmune disorders,²⁴ but this has not been supported by recent studies.²⁵⁻²⁷ However, chronic pelvic pain may be associated with autoimmune diseases.²⁸⁻³⁰ Taken together, this suggests that pelvic pains may have very different aetiologies, and that inflammatory signs are not only seen in endometriosis but also in other conditions. Treatment recommendations therefore differ.

Transmission of pain signals from the nociceptor terminal to the spinal cord

Pain is often considered to be a homogeneous sensory entity, mediated by a specialised high threshold sensory system, which extends from the periphery (nociceptors) through the spinal cord, brain stem and thalamus to the limbic structures, somatosensory and prefrontal cortices. When a pain condition becomes chronic there is an altered connectivity in the brain and this is also probably true in patients suffering from chronic endometrialgia.^{31:32}

Nociceptors have a high threshold and normally respond only to stimuli of sufficient energy potentially or actually to damage tissue.³³ The nociceptive neurone has four major functional components:

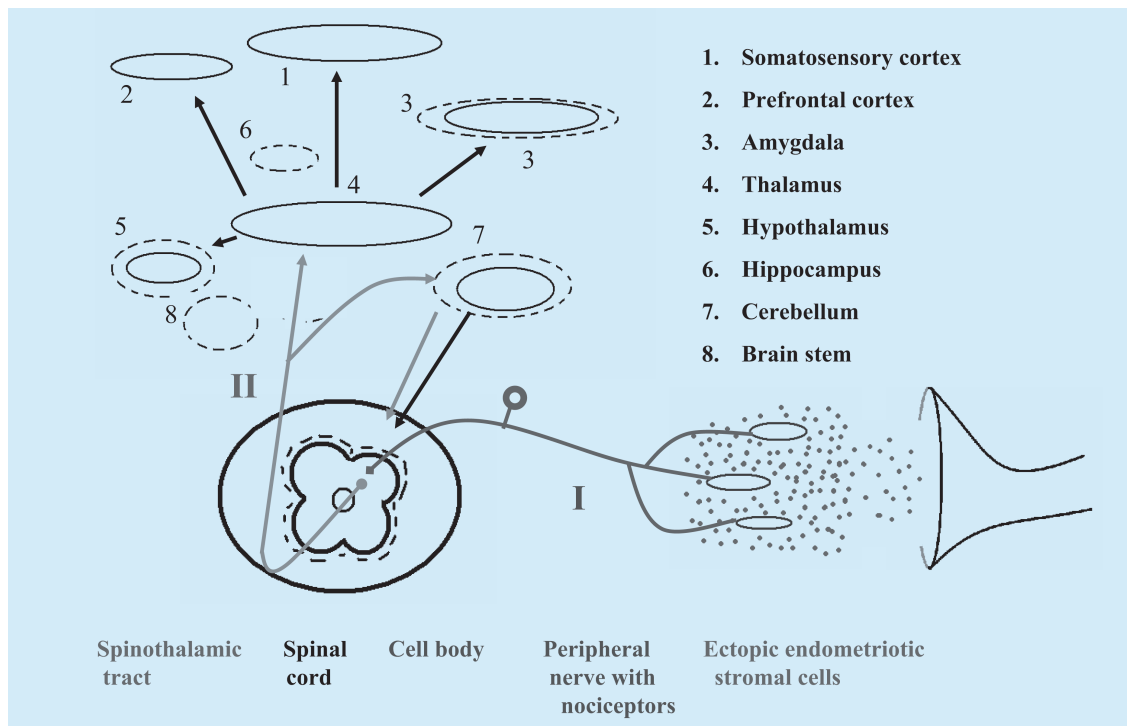


Figure 2 In this schematic illustration of the nociceptive system in endometrialgia, the primary (I) nociceptive neurone has four major functional components: the peripheral terminal that responds to external stimuli and initiates action potentials; the axon that conducts action potentials; the cell body that controls the identity and integrity of the neurone; and the central terminal which forms the presynaptic element of the first synapse in the sensory pathway in the CNS. The second order neurones (II) that extend from the dorsal horn of the spinal cord through the brain stem to the central nervous system's pain matrix (thalamus, amygdala, somatosensory and prefrontal cortices). When the endometrialgia becomes chronic altered connectivity is also seen in other parts of the brain including the hypothalamus, hippocampus and cerebellum.

Sensory processing is controlled through local segmental circuits in the dorsal horn of the spinal cord and by descending tonic and phasic inhibitory and facilitatory influences arising from the brain. Inhibition (or facilitation) may be mediated through presynaptic receptors on the central terminal of nociceptors or through postsynaptic inhibition on the second-order neurones.

- 1) the peripheral terminal that responds to external stimuli and initiates action potentials
- 2) the axon that conducts action potentials
- 3) the cell body (soma) that controls the identity and integrity of the neurone
- 4) the central terminal which forms the presynaptic element of the first synapse in the sensory pathway.

Some nociceptor afferents are thinly myelinated (A δ fibres) but most are unmyelinated (C fibres), and these slowly conducting afferents represent the majority of sensory neurones in the peripheral nervous system. Projection neurones (second order neurones) in the dorsal horn transfer nociceptive input to the brainstem, hypothalamus, and thalamus and then, through relay neurones, to the cortex (Fig 2).³⁴⁻³⁶

Nociceptors and peripheral sensitisation

There are two major classes of nociceptive neurones, *peptidergic* and *non-peptidergic*. During neurogenesis about half of the developing nociceptive neurones switch off the nerve growth factor (NGF) tyrosine kinase A (TrkA) receptor and begin to express Ret (rearranged during transfection), the transmembrane tyrosine kinase signalling component of the receptor for glial cell derived growth factor (GDNF) and other GDNF-related growth factors. These neurones become the non-peptidergic nociceptors, most of which bind isolectin B4 (IB4). The remaining nociceptors retain and develop into the peptidergic class of nociceptors that express the neurotransmitters calcitonin gene related peptide (CGRP) and substance P (SP) and do not bind IB4. A key factor in neurogenesis is played by the runt related transcription factor 1 (Runx 1). During nociceptor segregation the expression of Runx 1 persists in non-peptidergic cells but not in prospective TrkA-peptidergic cells. Interestingly, Runx 1 is selectively required for thermal but not mechanical pain sensitivity, supporting the idea that specification of nociceptive mechanical and thermal sensitivity is subjected to separate genetic control.³⁷

Nociceptors are found in most visceral tissues including the uterus and cervix.³⁸ 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.^{39,40} Findings in experimental and clinical studies suggest that these nerve fibres are nociceptors, invading peritoneal endometriotic lesions,⁴¹⁻⁴³ and are not present in women without endometriosis.⁴⁴ This has been interpreted as an abnormal sprouting of nociceptors in the endometrium and in peritoneal endometriotic lesions in women with endometriosis. Such nerve sprouting, if confirmed, is probably caused by increased levels of NGF and GDNF.^{18,45,46} The challenging hypothesis of a role of small unmyelinated nerve fibres in endometriosis needs to be confirmed. However, a recent experimental study supports the notion that endometriosis may be considered a neurovascular condition.⁴⁷

Several nociceptors in visceral tissues have been shown to have properties of 'silent nociceptors'.⁴⁸ These nociceptors are normally silent without responding to mechanical (pressure or distension) or thermal stimuli. When the surrounding tissue is inflamed, however, they become sensitised, ie change from being exclusively noxious stimulus detectors to detectors also of innocuous inputs (Fig 3a).^{49,50} One may speculate that this is also true for nociceptors found in the endometrial implants. The *peripheral sensitisation* represents a form of stimulus evoked functional plasticity of the nociceptor. Sensitising 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.⁵¹⁻⁵⁴ Among these are the transient receptor potential (TRP) channels. The TRP channels have emerged as a family of evolutionarily conserved ligand gated ion channels that contribute to the detection of physical stimuli. Six TRPs (TRPV1, TRPV2, TRPV3, TRPV4, TRPM8 and TRPA1) have been shown to be expressed in primary afferent nociceptors where they act as transducers for thermal, chemical and mechanical stimuli.^{55,56} (Fig 3a) These receptors are coupled to intracellular kinases, protein kinase A (PKA), protein kinase C (PKC), the mitogen activated protein kinases (MAPKs) extracellular signal regulated kinase (ERK) and p38 as well as the c-Jun amino-terminal kinase 1 (JNK), in the cytoplasm of the terminal.⁵⁷ The kinases phosphorylate amino acids, for example serine and threonine, which result in a change in the proteins

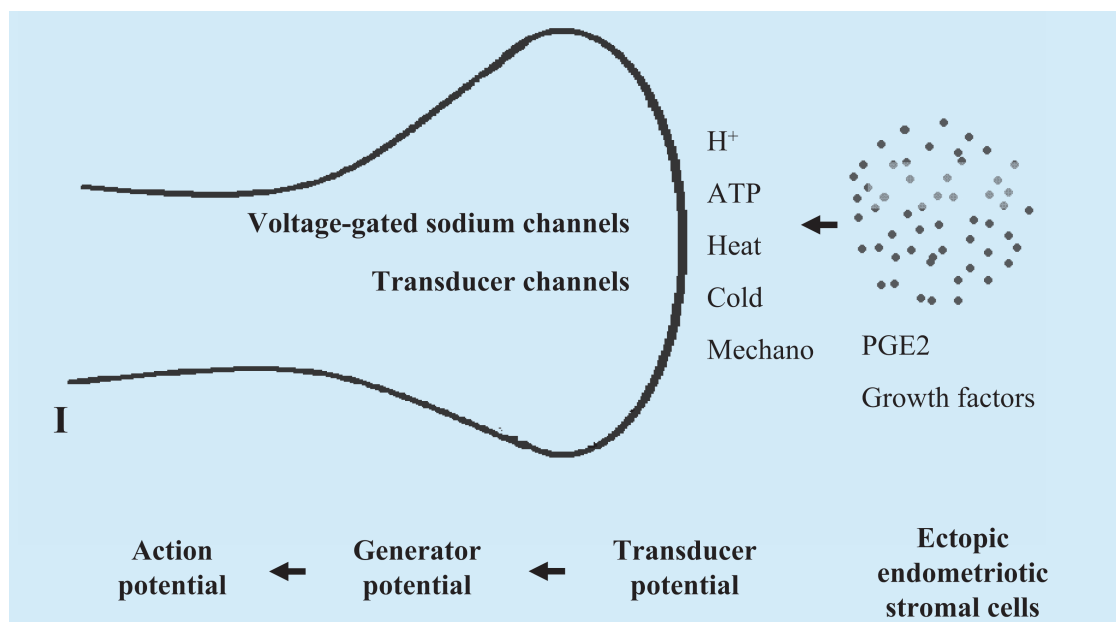


Figure 3 This schematic illustration of a peripheral nociceptor terminal shows endogenous compounds being released from the cystic tissue, eg 'inflammatory soup', and some of them act directly on the nociceptor to activate it. For example, release of adenosine triphosphatase (ATP) by ectopic stromal cells results in immediate activation of ligand gated purinoreceptors. Protons, in contrast, build up slowly and act on acid sensitive ion channels (ASICs) and transient receptor potential (TRP) channels. Other compounds (such as cytokines, chemokines, PGE2, bradykinin, and nerve growth factor) that are released sensitise the terminal so that it becomes hypersensitive – peripheral sensitisation – to subsequent stimuli via signal transduction pathways in the peripheral terminal, alterations in the trafficking and properties of transducer and sodium channels, largely as a result of phosphorylation.

produced (post-translational processing). Such phosphorylation may alter the activity of receptors and ion channels (TRPs and voltage-gated sodium channels) dramatically increasing membrane excitability. In addition to the kinases, the second messenger nitric oxide (NO) contributes to induction of pain and sensitisation. However, unlike the other second messengers, antinociceptive effects of NO are also reported. The exact function and interrelationship of the different second messengers in nociceptor signalling remains to be established as it remains unclear for the moment what determines the use of the varying signalling pathways in nociceptive neurones especially as most of them are polymodal, ie respond to multiple kinds of stimuli. Peripheral sensitisation results in hyperalgesia ie increased sensitivity in the receptive field of the nociceptive neurone (*primary hyperalgesia*).

Increasingly, the importance of non-neural cells and subcellular clustering, including lipid rafts, has attracted attention.³⁷ Lipid rafts are membrane patches

enriched in sphingomyelin and cholesterol based lipids, accumulating a large number of proteins. Following nociception, protein delocalisation toward or away from lipid rafts has been observed. Receptors involved in nociception, such as the β 2-adrenergic receptor, the bradykinin receptor 2, and the neurokinin receptors 1, have been found to be localised to membrane subdomains in non-neuronal cells.

In general, the transducer channels on the nociceptors are non-selective cation or sodium channels that are gated by temperature, chemical ligands, and mechanical shearing forces. Once they are activated, the channels open and sodium and calcium ions flow into the peripheral terminal of the nociceptor, producing an inward current that depolarises the membrane 'generator current'. If the depolarising current is sufficient to activate voltage gated sodium channels, they too will open, further depolarising the membrane and initiating a burst of action potentials in C or A δ fibre axons. The frequency and the duration of the action potential

bursts reflect the intensity and duration of the noxious stimulus.⁵⁸

A common aspect of endometrialgia is *spontaneous pain* (stimulus independent pain). This pain may hypothetically arise from signal molecules continuously released from the implants that act on nociceptor peripheral terminals to either produce a depolarisation 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 mechano-nociceptors. This spontaneous pain is transmitted in C fibres.

Dorsal root ganglion

The soma of the nociceptive neurones in the dorsal root ganglion keep themselves informed about the status of their peripheral terminals and the target tissue ie the endometriosis lesions. Peripheral inflammation, in addition to driving peripheral sensitisation, produces retrograde transport of signals, for example NGF activated Trk receptors, that

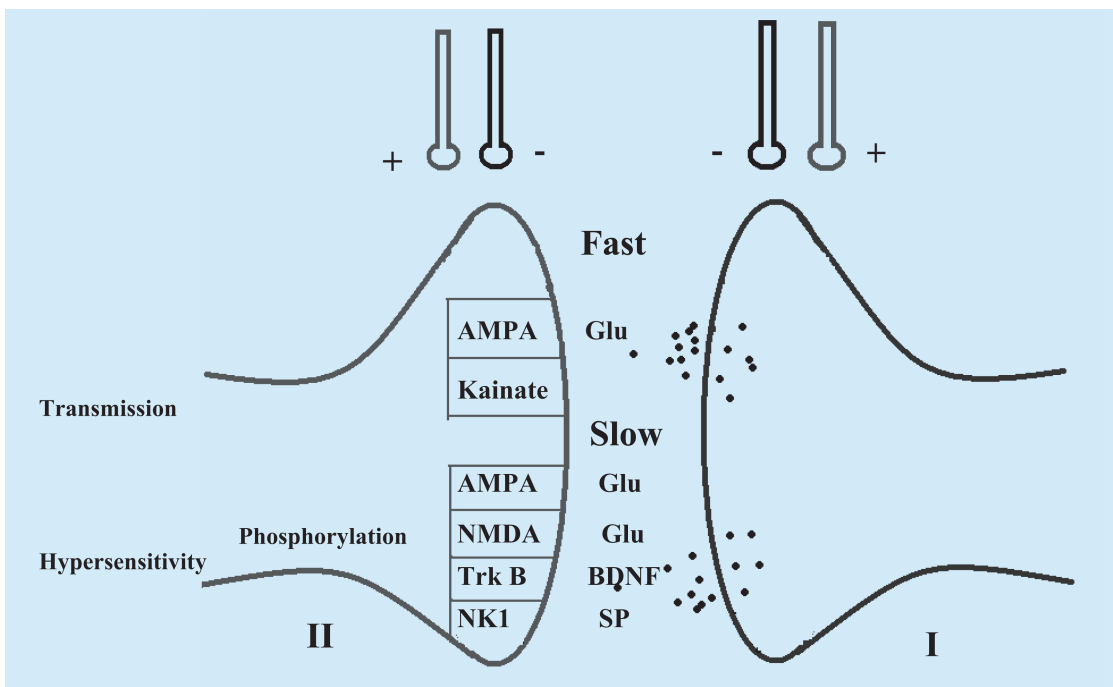


Figure 4 The transmission of nociceptive information and central sensitisation is shown here to be partly dependent on the activity in the first order neurone and the sensitivity of the second order neurone. Glutamate (Glu) is a major excitatory neurotransmitter in the central nervous system (CNS). Its receptors are classified as ionotropic receptors, which are ion channels and include alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainate and N-methyl-D-aspartic acid (NMDA) receptors, named after the agonists that selectively bind to them, and metabotropic receptors, which are G-protein coupled receptors. The peptide substance P (SP) and its tachykinin receptor, neurokinin-1 (NK1) and the brain derived neurotrophic factor (BDNF) and its tyrosine kinase (Trk) B receptor also result in the activation of G-protein coupled receptors. Activation of G-protein receptors results in release of calcium from intracellular supplies and protein kinase and phospholipase activation.

Central sensitisation is partly driven by high levels of nociceptive input that, via transmitter release and action on the multiple receptors expressed on the second order projection neurones in the dorsal horn, results in activation of intracellular kinases that phosphorylate ion channels and receptors, altering their distribution and function and thus increasing excitability and pain sensitivity. Central sensitisation also involves changes in transcription in the second order neurones. Some alterations in gene expression are restricted, others are widespread, like the induction of COX-2 after peripheral inflammation. After a peripheral nerve lesion, there is a loss of GABA interneurones, resulting in a loss of inhibition producing pain hypersensitivity.

increase in the cell body the transcription of neuropeptides, brain derived neurotrophic factor (BDNF), and sodium channels. There is also an increased translation of TRPs channels augmenting both peripheral sensitisation and central transmission.^{58,59}

In the soma, the protein kinase PKC ϵ plays a key role in the long lasting pain, through maintenance of a primed state. It has been suggested that three neuronal states can be differentiated in the nociceptive neurone, the *naïve*, the *primed*, and the *hyperalgesic state* (Fig 4).

Exposure of naïve neurones to inflammatory stimuli results in sensitisation of the nerve, ie hyperalgesia. This hyperalgesic state lasts for a few hours. However, even though the sensitivity partly decreases it remains increased for weeks ie in a primed state. Interestingly, hyperalgesia induced from the primed state is markedly prolonged as compared to the naïve state. This could explain 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 PKC ϵ dependent. If in the primed

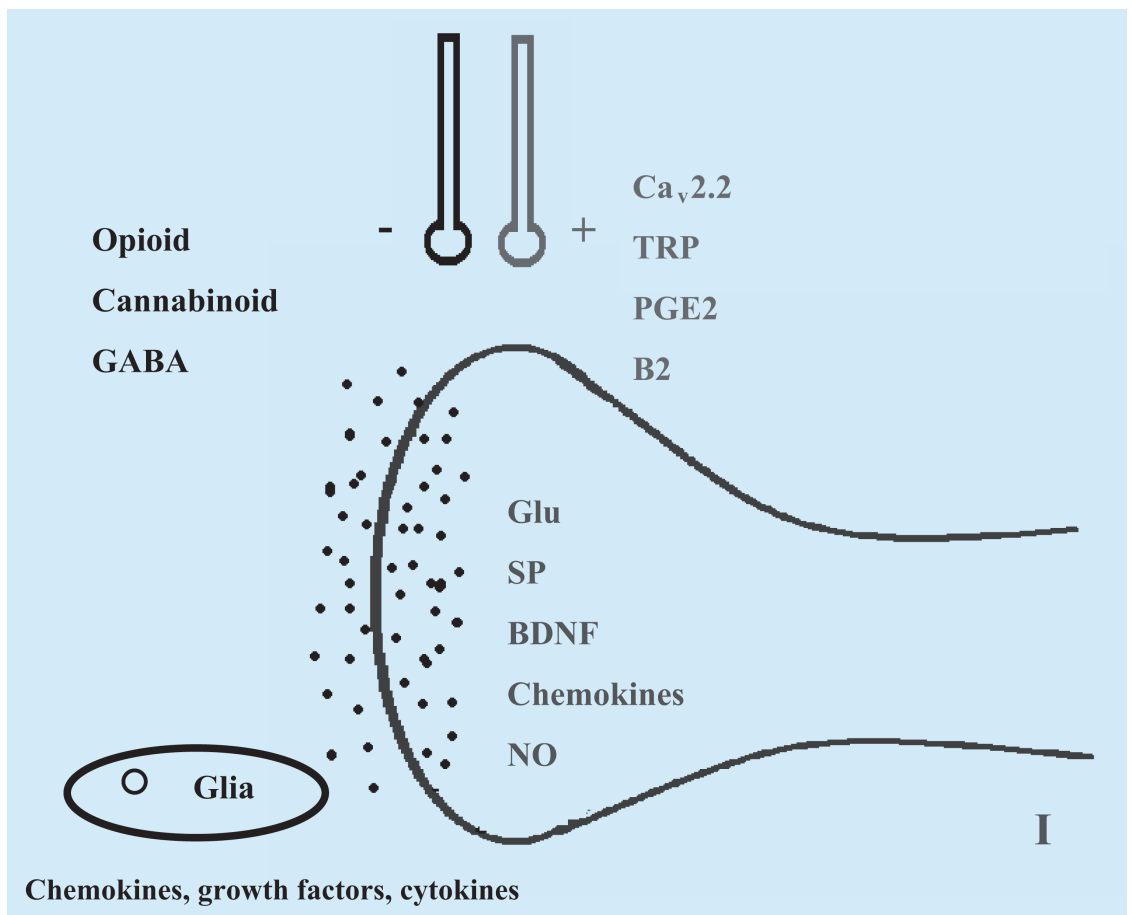


Figure 5 Transmission in the central nociceptor terminal occurs in response to calcium influx at the central terminal releasing glutamate as well as multiple synaptic modulators – neurotransmitters such as substance P (SP) and growth factors such as brain derived neurotrophic factor (BDNF) and signalling molecules (chemokines). The terminal is subjected to both excitatory (presynaptic facilitation) and inhibitory (presynaptic inhibition) influences. Activity mediated by opioid, cannabinoid and gamma-aminobutyric acid (GABA) receptors inhibits the release of neurotransmitters whereas activity mediated by calcium, transient receptor potential (TRP), PGE2 and bradykinin 2 (B2) receptors on the central terminal of the nociceptive neurone, enhance the release. Nitric oxide (NO) and chemokines released from the central terminal interact with glial cells, releasing proinflammatory compounds, in the dorsal horn of the spinal cord. Modified from Woolf and Ma.⁵⁸

neurone PKC ϵ is blocked the neurone returns to the naïve state.³⁷

As endometriosis patients often undergo surgery there is a theoretical risk that the peripheral axon of nociceptor afferents is damaged. If the peripheral axon is damaged marked changes in transcription may occur in the soma. Some of these represent attempts by the neurone to survive, others are attempts for the axon to re-grow, but many changes are maladaptive and produce alterations in function that can possibly drive visceral pains like endometrialgia probably as a form of neuropathic pain. 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.⁶⁰ This ectopic excitability contributes to spontaneous pain. Ectopic firing may also originate from the DRG (dorsal root ganglion) neurones. This firing may be attributed to neighbouring intact fibres in the DRG that have been exposed to cytokines such as tumour necrosis factor alpha (TNF α) produced by deafferented Schwann cells.⁶¹

Transmission of pain signals in the dorsal horn of the spinal cord

The central terminals of the nociceptive neurones are located in the dorsal horn of the spinal cord. These terminals transfer synaptic input to second order neurones that project to the thalamus through the spinothalamic tract.⁶²

Central terminal of nociceptors

The central terminals transfer nociceptive information through the neurotransmitter release of glutamate, SP, CGRP and BDNF. The release is dependent on the calcium influx in the central terminals of the nociceptive neurones. The calcium influx is dependent on the frequency and duration of the action potentials and modulating factors.⁶³ The major voltage gated calcium channel in the central terminal of the nociceptors is Ca_v2.2. Inhibiting factors, which decrease transmitter release (and thereby nociceptive transmission), include endogenous opioids (β -endorphin, enkephalin, dynorphin) acting on μ -, δ - and κ -opioid receptors, GABA on GABA B receptors, and endogenous cannabinoids on CB receptors.⁶⁴ Facilitating factors, which increase

transmitter release, include PGE2 and bradykinin acting via their G-protein coupled B2 receptors.⁵⁸ (Fig 5)

In addition to regulating the flow of information by transmitter release, nociceptor neurones 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.

Structural reorganisation

In healthy women without pain the central terminals of nociceptor sensory neurones terminate in the most superficial laminae of the dorsal horn whereas the low threshold sensory fibres activated by touch, pressure, or vibration terminate in the deep laminae. One may speculate that in women with endometriosis, and a peripheral nerve injury, there is a new growth and/or sprouting of the central terminals of the low threshold afferents into the zone normally occupied exclusively by the nociceptor terminals. Such a phenomenon could possibly explain the intractability reported by some patients with neuropathic pain conditions.^{65,66}

Transmission

Transfer of input from nociceptors to neurones in the dorsal horn of the spinal cord that project to the thalamus is mediated by direct monosynaptic contact or through multiple interneurons, some of which are excitatory and some inhibitory.

The monosynaptic activation is fast. The fast excitatory synaptic potentials are mediated by the release of the excitatory amino acids (like glutamate) and their action on ligand gated ion channel receptors on the postsynaptic membrane of the central neurones.⁶²

Intense stimulation also results in the release of neuropeptides, such as CGRP and SP and BDNF. The neuropeptides act on G-protein coupled receptors to produce slow, more sustained synaptic currents than does glutamate, and BDNF acts on Trk B receptors to modify membrane excitability. Neuropeptide mediated 'slow' synaptic potentials, together with the activation by glutamate of the N-methyl-D-aspartic acid (NMDA) receptor, results in activity dependent and/or use dependent plasticity. At resting membrane potentials, the NMDA receptor ion channel is blocked by a magnesium ion so that no current flows if glutamate binds to the receptor;

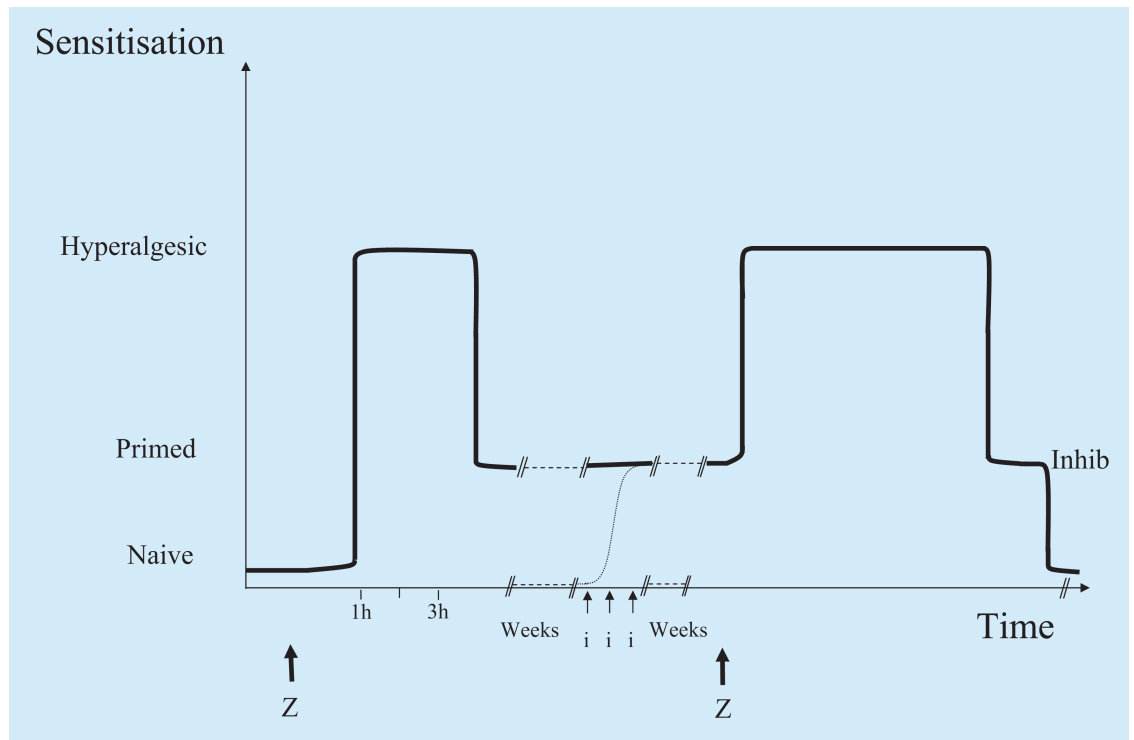


Figure 6 Three modes of sensitivity have been differentiated in the nociceptive neurone; naïve, primed, and hyperalgesic. Noxious stimuli (Z) of the naïve neurone result in hyperalgesia. This state lasts for 1-5 hours. Thereafter the sensitivity to physical stimuli returns to the naïve stage while the sensitivity to successive inflammatory stimuli remains increased ie in a primed state. A primed state may last for weeks and is also seen after light repeated exposure to inflammatory mediators (i). If the nociceptive neurone is challenged when in a primed state the hyperalgesia induced is markedly prolonged. The primed state may be inhibited (inhib) of PKC ϵ , modified from Hucho and Levine.³⁷

activation of the NMDA receptor by glutamate produces excitation only when this block is relieved by depolarisation (Fig 6).⁶²

Central sensitisation and activity dependent plasticity

Central sensitisation begins with a cascade of events in the dorsal horn of the spinal cord. One key receptor involved in these changes is the glutamate activated NMDA receptor. During central sensitisation, this receptor is phosphorylated, which increases its distribution from intracellular stores to the synaptic membrane and its responsiveness to glutamate. The increase in excitability of the secondary neurones means that they can be activated by inputs that are normally subthreshold and that their response to suprathreshold inputs increases.⁶² The recruitment of subthreshold inputs manifests as a lowered threshold for the eliciting of pain (innocuous stimulation becomes noxious, eg allodynia), an

exaggerated or amplified response to noxious stimuli (hyperalgesia), and the spread of sensitivity to non-injured areas (secondary hyperalgesia).

Inhibition of the NMDA receptor by using the competitive NMDA receptor antagonist ketamine reduces the early phase of central sensitisation and the resultant hypersensitivity to pain. One form of activity dependent plasticity is a progressive increase in the output from dorsal horn neurones in response to closely timed repeated input; this phenomenon, known as 'wind up', represents a form of pain amplification and is responsible for the increasing pain experienced in response to closely repeated stimulation. In vivo electrophysiological recordings have shown that elevated acid sensing ion channel (ASIC1a) activity is required for two forms of central sensitisation: C fibre induced wind up and antigen induced hypersensitivity of dorsal horn nociceptive neurones. Specific blockade of Ca²⁺ permeable ASIC1a channels thus may have anti-nociceptive

effect by reducing or preventing the development of central sensitisation induced by inflammation.^{67,68}

This may hypothetically also be true in endometriosis.

Early, activity dependent, post-translational changes occur in gene regulation, including the induction of new proteins and effects on the levels of expression of existing proteins. Some of the changes in gene expression are driven by synaptic mediated activation of intracellular signal transduction pathways and are restricted to parts of the nervous system that receive inputs from the inflammatory tissue. Other genes are more widely activated. COX-2, for example, begins to be expressed in (neuronal and non-neuronal) tissues, including the CNS, several hours after a localised peripheral tissue injury or inflammation.^{69,70} This expression is initiated by circulating humoral factors. Microglia probably play a key role in the synthesis of these cytokines and chemokines. These factors enter the cerebrospinal fluid and act on dorsal horn neurones resulting in PGE2 synthesis and increased excitability, which contributes to a late onset, prolonged, and diffuse phase of central sensitisation.⁷¹ The widespread central induction of COX-2 contributes to the generalised 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 may 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 humorally mediated central induction of COX-2 and may need to be supplemented by therapy with COX/COX-2 inhibitors.⁶²

Viscerovisceral reflexes

Clinical observations of viscerovisceral referred pain in patients with gastrointestinal and genitourinary disorders suggest an overlap of neurohumoral mechanisms and underlying visceral organ dysfunction.⁷² Cross-sensitisation among pelvic structures may contribute to chronic pelvic pain.⁷³ Convergence of sensory information from discrete pelvic structures occurs at different levels of nervous

system hierarchy including dorsal root ganglia, the spinal cord and the brain. In a recent experimental study in rats it was demonstrated that vaginal hyperalgesia in endometriosis is due to oestrogen sensitive implants.⁷⁴ These implants are innervated by autonomic and sensory nerve fibres.⁴¹ This supply connects the implants directly with the central nervous system via the splanchnic and vagus nerves suggesting that the vaginal hyperalgesia involves viscerovisceral interactions. Also, activity in the sympathoadrenergic system and its modulation by vagal afferents can have a powerful impact on the pain and inflammatory response.⁷⁵

From nociceptive projection neurones in the spinal cord to the brainstem, hypothalamus, thalamus and cortex

Projection neurones 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 neurones, to the cortex.⁷⁶ Supraspinal brain mechanisms are increasingly recognised as playing a major role in the representation and modulation of the pain experience.³⁵ Functional imaging and positron emission transmission scanning have shown that acute pain activates primary and secondary somatosensory (S1 and S2), insular (IC), anterior cingulate (ACC), and prefrontal cortices (PFC) 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.⁷⁷

Human brain imaging has provided new insights into how different psychological states affect pain.⁷⁸ 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.⁷⁹ 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.⁸¹

Disinhibition

Powerful tonic and phasic inhibitory events, acting pre- and post-synaptically, 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 neurones that release the inhibitory neurotransmitters glycine and GABA. Descending inhibitory inputs from the brainstem operate through norepinephrine and serotonin containing neurones.³⁵ It has been suggested that pathologic loss of inhibition (disinhibition) can lead to increased excitability and pain. This suggestion is supported by the finding of hypersensitivity to pain following the injection of receptor antagonists directed towards the receptors of GABA and glycine, indicating that ongoing inhibition substantially affects the function of the pain system.⁶²

Peripheral nerve injury results in substantial loss of inhibitory currents, particularly those mediated by GABA, and administration of GABA-mimetics reduces neuropathic pain. This suggests that disinhibition may possibly also contribute to hypersensitivity in patients with endometrialgia. One cause of such disinhibition is a selective death of GABA-ergic inhibitory interneurons after nerve injury. One week after a nerve injury that produces hypersensitivity to pain, neurones begin to undergo apoptosis in the dorsal horn. The apoptosis may be excitotoxic, due to excessive glutamate release or failure of glutamate uptake, or may result from cell death-inducing signals, such as the release of TNF α from activated microglia.

Pain and hormones in endometriosis

It is possible that the impact of oestrogen on nociceptors is central to why endometriosis causes the regional pain syndrome of chronic pelvic pain. Endometriosis is oestrogen dependent, and traditional treatments have aimed at decreasing the production of oestrogen such as oestradiol.⁸² Interestingly, Hudelist and collaborators have reported that there is a differential oestradiol production of endometrium as compared to endometriosis lesions.⁸³ Both oestrogen and androgen receptors are present in DRG

neurones.^{84:85} As stated above, PKC ϵ plays a key role in the primed state of sensitisation. In female rats, β 2-adrenergic receptor mediated sensitisation does not require PKC ϵ ,⁸⁶ but is dependent on systemic oestrogen levels. A similar dependency was found at the cellular level, establishing that oestrogen is able to act on the nociceptive neurone directly.⁸⁷ Surprisingly, in cultured DRG neurones, the action of oestrogen is very fast. One minute of preincubation with oestrogen abolishes the translocation of PKC ϵ in cultured, male derived sensory neurones, suggesting that a transcription independent mechanism is involved. Fast actions of sex hormones have also been shown in other systems.⁸⁸ Such fast concentration changes might have a physiological role in pain pathways. The oestrogen producing enzyme aromatase has been shown to be present in the spinal dorsal horn of male quails, at sites where peripheral nociceptive neurones terminate.⁸⁹ Aromatase activity was recently found to be involved in the establishment of thermal nociceptive threshold.⁸⁹ The oestrogen producing enzyme and the oestrogen receptors being adjacent to each other opens the possibility that concentration changes occur rapidly but only on a very local level, and therefore might not be reflected in changes of the more constant plasma levels. Thus, hormones could potentially have fast and local regulatory functions beyond their classical organism wide actions on gene transcription. Recently, Stratton and collaborators evaluated whether six months of treatment with raloxifene (a selective oestrogen receptor modulator) was effective in the treatment of chronic pelvic pain in women with endometriosis.⁹⁰ Raloxifene significantly shortened the time to return of chronic pelvic pain. Because recurrence of endometriosis lesions did not correlate with return of pain, other factors were suggested to be implicated in pelvic pain. Interestingly, oestrogens also stimulate production of prostaglandins,⁸ and increase levels of NGF in the uterus,¹⁵ hypothetically promoting sensitisation and nerve sprouting.⁹¹

Reducing oestrogen levels with gonadotrophin hormone analogues may lessen endometriosis pain,⁹² even when used concurrently with hormone replacement therapy. Another option is to use aromatase inhibitors which prevent oestrogen biosynthesis within the endometriotic lesion.⁹³ However, trials of raloxifene were closed due to an

unfavourable outcome and trials of fulvestrant (an oestrogen receptor antagonist) have remained unreported.⁹⁴

Pain management of endometriosis

Presently, most treatment has been aimed at the endometriosis lesion using laparoscopic excision or ablation and pharmacological treatments with GnRH agonists, synthetic pro-gestational hormones or danazol.⁹⁵⁻⁹⁷ The aim of the hormonal suppressive therapy is to induce a downregulation of the hypothalamo-pituitary-ovarian pathway. Progestins (such as oral norethindrone or depot medroxyprogesterone) are commonly used. If the pain is associated with menses or deeply infiltrating rectovaginal lesions, intrauterine levonorgestrel has proven to be effective. In severe cases gonadotropin releasing hormone agonists have been tried, sometimes with progestins to reduce drug related symptoms. However, these medications, which aim to lower oestrogen levels, even if effective in most patients, do not always alleviate pain and may have significant side effects.⁹⁸⁻¹⁰³ The recurrence of painful symptoms is high both after medical treatments and after laparoscopic surgery,¹⁰⁴ and pain is known to persist or recur even after complete excision of endometriosis lesions.¹⁰⁵ This strongly suggests that other aspects of pain are present and that surgical excision and suppression of oestrogen is not sufficient in the management of such pain.¹⁰⁶ Possibly, herbal drugs may prove to be efficacious complements.^{28:107}

Endometriosis also results in sensitisation of nociceptors with one of the main contributing factors being the prostanoid PGE2.¹⁰⁸⁻¹¹⁰ NSAIDs and COX inhibitors have an analgesic action in such chronic endometriosis where COX-2 is expressed chronically as a result of maintained inflammation. Because several sensitisers are present (PGE2, NGF and bradykinin), blocking the production of only one of these substances singly at any time will not eliminate peripheral sensitisation. This factor contributes to the ceiling effect of such drugs as COX-2 inhibitors.

Inhibition may be mediated through presynaptic receptors on the central terminal of nociceptors or through postsynaptic inhibition. The presynaptic receptors can reduce the transmitter release and serve as a major site for the action of opioids, cannabinoids (CBs), GABA receptor ligands, and the anticonvulsants gabapentin and pregabalin.¹¹¹⁻¹¹³

Postsynaptic inhibition involves a hyperpolarising inhibitory potential evoked in dorsal horn neurones by the opening of potassium or chloride channels in response to opioids and GABA.

However, NSAIDs and COX-2 inhibitors do not offer any benefit to patients whose endometrialgia is due mainly to ectopic excitability caused by abnormal sodium channel activity after nerve injury (neuropathic pain).¹¹⁴ In these patients amitriptyline and/or gabapentin could be tried as well as tramadol and meptazinol.¹¹⁵ Pregabalin has also been tried in patients with endometrialgia. Pregabalin is a new synthetic molecule and a structural derivative of the inhibitory neurotransmitter GABA, an $\alpha\delta$ ligand that induces analgesic, anticonvulsant, anxiolytic, and sleep modulating effects. Pregabalin binds potently to the $\alpha\delta$ subunit of calcium channels, resulting in a reduction in the release of several neurotransmitters.¹¹⁶

Descending pain inhibition is activated by acupuncture or moxibustion (heat stimulation) as well as by expectation.¹¹⁷⁻¹¹⁸ Counter irritation and low threshold afferent inputs (vibratory stimulation, transcutaneous electrical nerve stimulation, TENS, or massage) may also activate inhibitory mechanisms at the spinal cord level.¹¹⁹ In models of inflammation, inhibition of δ -opioid receptors prevents antihyperalgesia produced by high frequency stimulation, whereas inhibition of μ -opioid receptors prevents antihyperalgesia produced by low frequency stimulation, suggesting that both modalities may be tried in endometrialgia.¹²⁰ In severe cases spinal cord stimulation may be an option.¹²¹

Depression and painful somatic symptoms commonly occur together. It has been suggested that patients with chronic endometrialgia display depressive symptoms.¹²² The brain stem serves as an important connection between the higher brain centres and the spinal cord. In the brain stem, the neurotransmitters serotonin and norepinephrine modulate pain transmission through ascending and descending neural pathways. Both serotonin and norepinephrine are also key neurotransmitters involved with the pathophysiology of depression. Tricyclic antidepressants are effective treatments for pain and depression; selective serotonin reuptake inhibitors provide less benefit. Duloxetine and venlafaxine, which are serotonin and norepinephrine reuptake inhibitors, have been shown to alleviate

pain and depressive symptoms. Neuropathic pains as well as chronic pain syndromes (functional pains) were also shown to benefit from duloxetine and venlafaxine. Their extended use in chronic endometrialgia should be recognised.¹²³

Finally, endometrialgia may, besides being associated with pain, also be associated with insufficient coping strategies,²³ and comorbidity,¹²⁴⁻¹²⁶ suggesting that patients with these symptoms may benefit from the services of a multiprofessional pain rehabilitation team with access to a multitude of interventions and support for the alleviation of their endometriosis pain as well as related impairments and disabilities. Cognitive behavioural interventions are the most extensively researched form of psychological treatment and are increasingly offered through the internet. Internet delivered cognitive behavioural interventions are a promising addition and complement to existing treatments.¹²⁷

Acupuncture in pelvic pain

We have recently reported on pelvic pain in women and the possible use of acupuncture in these conditions.¹¹⁷ In 2006 Highfield and coworkers presented two case reports describing the impact of a course of acupuncture on adolescent girls with endometriosis related chronic pelvic pain of more than one year.¹²⁸ Both patients, undergoing between 9 and 15 treatments over a 7 to 12 week period, experienced modest improvement in pain, as well as self or family reported improvement in headaches, nausea and fatigue. No adverse effects were reported. The authors conclude that acupuncture may be an acceptable and safe adjunctive therapy for some adolescents with endometriosis related pelvic pain refractory to standard endometriosis treatments.

Social support and distraction

Nazik Al-Malaika was an Iraqi female poet and is considered by many as one of the most influential contemporary Iraqi female poets and the first Arabic poet to use free verse. Towards the end of her life, Al-Malaika suffered from a number of health issues including pain. In her *Five Hymns Toll Pain* she emphasises social support and distraction: 'Can we not conquer pain, postpone it to another day, keep it busy one evening, divert it with a game, a song, a forgotten ancient tale'.

Conclusions

Endometriosis is a common cause of pelvic pain in women and the pain is often incapacitating. Endometriosis pain can have different causes such as inflammatory, neuropathic and functional and may thus be triggered by different mechanisms. Endometrialgia may be evoked by a low intensity, normally innocuous stimulus (allodynia), or it may be an exaggerated and prolonged response to a noxious stimulus (hyperalgesia). Endometrialgia may also arise spontaneously in the apparent absence of any peripheral stimulus.

Oestrogen and prostanoids probably play a key modulatory role in endometrialgia. Consequently, NSAIDs and oral contraceptives are often used as an initial approach.¹²⁹⁻¹³¹ In some patients surgical removal of ectopic growths or the uterus as well as denervation are tried.¹³² Apart from the above interventions, opioids and opioid analogues as well as antidepressants and anticonvulsants have been used with some success. Also, in some women, sensory stimulation techniques (acupuncture or TENS) as well as cognitive therapy may be tried as adjunctive treatments.

Conflict of interest

TL chairs the charity 'The Foundation of Acupuncture and Alternative Biological Treatment Methods' which has received grants from AKAB Utbildning AB to support acupuncture research. IL is funded for research into acupuncture and has no link with a commercial organisation. This article was externally peer reviewed.

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