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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

inhibitory inputs from the brain stem operate through norepinephrine and serotonin containing neurons Ren and Dubner [90]. 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 [84].

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, neurons 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 TNFα- from activated microglia.

8. Role of hormones in endometriosis pain

Endometriosis is estrogens-dependent, and traditional treatments have aimed at decreasing the production of estrogens such as estradiol [33]. Both estrogens and androgen receptors are present in DRG neurons (McRoberts et al. [93]; Patrone et al. [94]). In female rats, β2-adrenergic receptor-mediated sensitization does not require PKCϵ Dina et al. [95]. This phenotype is dependent on systemic estrogens levels. A similar dependency was found at the cellular level, establishing that estrogens are able to act on the nociceptive neuron directly [32]. Surprisingly, in cultured DRG neurons, the action of estrogens is very fast. One minute of preincubation with estrogens abolishes the translocation of PKCϵ in cultured, male-derived sensory neurons, suggesting that a transcription-independent mechanism is involved. Fast actions of sex hormones have also been shown also in other systems Falkenstein et al. [96]. Such fast concentration changes might have a physiological role in pain pathways. The estrogens-producing enzyme aromatase is present in the spinal dorsal horn, at sites where peripheral nociceptive neurons terminate Evrard and Balthazart [97]. Aromatase activity was recently found to be involved in the establishment of thermal nociceptive threshold Evrard and Balthazart [97]. The estrogens-producing enzyme and the estrogens 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. Estrogens also stimulate production of prostaglandins Giudice and Kao [98] and increase levels of NGF in the uterus Shi et al. [99] thereby promoting sensitization and nerve sprouting Pezet and McMahon [100].

Reducing estrogens levels with gonadotrophin hormone analogues may lessen endometriosis pain Moghissi et al. [101] even when used concurrently with hormone replacement therapy. Another option is to use aromatase inhibitors which prevent estrogens biosynthesis within the endometriotic lesion and or spinal cord Attar and Bulun [102]. However, trials of raloxifene (a selective estrogens receptor modulator) were closed due to an unfavourable outcome and trials of fulvestrant (an estrogens receptor antagonist) have remained unreported Guo and Olive [103].

9. Clinical description of the endometriosis pain

The perceived pain is often described as dull, throbbing, sharp, burning, and exacerbated by physical activity [12,8,6,43]. Clinical signs of the sensitized nerve function can be present as hyper phenomena like perceived pain in response to non-noxious stimulation, allodynia, and or exaggerated pain responses to minor noxious stimuli, hyperalgesia [84]. Other reported clinical signs of sensitization are local myofascial dysfunction in terms of muscular trigger points and lowered pain thresholds in the pelvic area [68]. Depending on its pathophysiological source, the endometriosis related pain can be categorized as inflammatory, caused by inflammatory or ischaemic reactions in local tissue, or neuropathic, owing to secondary local nerve lesions such as nerve distortion, compression or damage [3]. In both categories can regional allodynia and hyperalgesia be present [84] meaning increased sensitivity to external stimulation.

The pain sensation is usually described as its intensity/severity but is defined also by its other aspects like perceived unpleasantness and thoughts affecting the overall life reflecting how pain impulses activate different areas of the brain. To address these different aspects of pain is of importance in diagnostic assessment, and in choice and evaluation of treatment.

10. Treatment of endometriosis pain

Since endometriosis related changes may exacerbate symptoms and possibly predispose for other long-lasting pain conditions [12] pain alleviation strategies is of greatest importance. The present offered therapies aims to influence different mechanisms and often consists of pharmacological treatments such as non-steroidal anti-inflammatory drugs, NSAIDs, anti-estrogens, gonadotropin-releasing hormone agonists, GnRH, and surgical removal of lesion-invaded tissue. However, many of these interventions do not generally manage the perceived pain sufficiently and have significant side effects [81]. Furthermore, recurrence of painful symptoms after both pharmacological and surgical treatments have been reported [25,1,20].

Non-pharmacological treatment strategies based on sensory stimulation could therefore be an alternative to be tried out. The pain alleviating effects induced by sensory stimulation like acupuncture techniques has been described as inducing several physiological and psychological changes such as activating endogenous descending pain inhibitory systems, deactivating brain areas transmitting sensations of unpleasantness and by inducing expectation of symptom relief [5,34]. Although, widely used to manage long-term pain [16], acupuncture remains controversial, partly due to the lack of explanation of a clear mechanism of pain alleviation. However, it has been described as potent for different long-term pain condition [78,79] in comparison with various control conditions [46] and safe as a pain alleviating treatment procedure provided that it is carried out by skilled therapists [44,83].

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. This study reports on the effects of acupuncture on endometriosis pain.

Ideally, all treatments should be individually tailored based on the individual's specific symptom as pain is perceived different between individuals and as the same type of symptom may have different implications for different women [71]. Therefore both individual as well as the group responses have been assessed.

11. Method and results

This review assessed 3 reports on acupuncture in endometriosis pain [30,75,61]. Two of the studies [75] were performed as prospective randomized single blind placebo/sham designs. The third study [30] was a retrospective observational case series study. In the studies the patients rated pain intensity was the primary outcome variable.

In total were 121 women with endometriosis pain were enrolled. The needle insertions per subject and treatment session were 7–12 and the needle retention time described as 15–25 min. The most commonly used points were CV4, CV6, SP6, SP10, KI3, PC6 and ST36.

The number of treatments varied from 9 to 16 among the three studies and the treatment frequency was presented as twice a week in works by Rubi-Klein and Wayne while Highfield and collaborators described that as in average a little bit more than once per week. Continuation with regular analgesic intervention was reported in two of the studies (Rubi-Klein and Highfield).

In all three studies the patients rated their pain intensity lower after acupuncture treatment, regardless of technique as compared to before start of the treatment period. Decrease of analgesic intake and perceived stress within the acupuncture treated groups were reported in the studies of Rubi-Klein and Wayne respectively. In the observational study by Highfield the social activity and attendance in school activity were reported as increased after the treatment period. Systematic differences between the treatment group and control group in evaluation of rated pain intensity was demonstrated in the Rubi-Klein study. A similar trend between the treatment and control group was seen in the study by Wayne and collaborators.

12. Discussion and conclusion

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.

Many of the current medical treatments for it include oral drugs like non-steroid anti-inflammatory drugs, opioids, antidepressants, anticonvulsants, 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.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arthe.2015.08.003.

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