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Nerve fibers and endometriotic lesions: partners in crime in inflicting pains in women with endometriosis

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ABSTRACT

One of major objectives in treating endometriosis is to alleviate pain since dysmenorrhea and other types of pain top the list of complaints from women with endometriosis who seek medical attention. Indeed, endometriosis-associated pain (EAP) is the most debilitating of the disease that negatively impacts on the quality of life in affected women, contributing significantly to the burden of disease and adding to the substantial personal and societal costs. Unfortunately, the mechanisms underlying the EAP are still poorly understood. In the last two decades, one active research field in endometriosis is the investigation on the distribution and genesis of nerve fibers in eutopic and ectopic endometrium, and the attempt to use endometrial nerve fiber density for diagnostic purpose. Since EAP presumably starts with the terminal sensory nerves, in or around endometriotic lesions, that transduce noxious mediators to the central nervous system (CNS) which ultimately perceives pain, this field of research holds the promise to elucidate the molecular mechanisms underlying the EAP, thus opening new avenues for novel diagnostics and therapeutics. In this review, we shall first briefly provide some basic facts on nerve fibers, and then provide an overview of some major findings in this filed while also note some conflicting results and expose areas in need of further research. We point out that since recently accumulated evidence suggests that endometriotic lesions are wounds undergoing repeated tissue injury and repair, the relationship between endometriotic lesions and nerve fibers is not simply unidirectional, i.e. lesions promote hyperinnervations. Rather, it is bidirectional, i.e. endometriotic lesions and nerve fibers engage active cross-talks, resulting in the development of endometriosis and pain. That is, nerve fibers and endometriotic lesions are actually partners in crime in inflicting pains in women with endometriosis, aided and abetted possibly by other culprits, some yet to be identified. We provide a list of possible perpetrators likely to be involved in this crime. Finally, we discuss possible implications when viewing the relationship from this vista.

Introduction

One of major objectives in treating endometriosis is to alleviate pain [1] since dysmenorrhea and other types of pain top the list of complaints from women with endometriosis that prompt them to seek medical attention. Indeed, endometriosis-associated pain (EAP) is the most debilitating of the disease that negatively impacts on the quality of life in affected women [2,3], contributing significantly to the burden of disease and adding to the substantial personal and societal costs due to symptom-related reduced productivity [4,5]. While a great deal is known of the molecular, hormonal, cellular, and immunological aspects of endometriosis thanks to extensive research in the last few decades, the mechanisms underlying the EAP are still poorly understood [6]. In fact, the precise relationship between the pain severity and various characteristics of endometriosis has not been well established and is often a matter of conflicting reports [7–12].

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [13]. As endometriosis is a disease with identifiable lesions [14], the sensation of EAP presumably starts with sensory nerves that transduce noxious mediators, secreted by lesions and other cells in their microenvironment, to the central nervous system (CNS) which ultimately perceives pain. While women with endometriosis manifest central sensitization [15], are possibly associated with altered brain structure, chemistry, and

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function in pain processing regions [16,17], and may also have sustained activation of descending pain facilitatory pathways from the brainstem [18], so far much effect in EAP research is focused on the identification of nociceptors in general and nerve fibers in particular.

In this review, we shall first briefly provide some basic facts on nerve fibers, and then provide an overview of some major findings in this filed while also note some conflicting results and expose areas in need of further research. We point out that since accumulating evidence suggests that endometriotic lesions are wounds undergoing repeated tissue injury and repair (ReTAIR) [19–21], the relationship between endometriotic lesions and nerve fibers is not simply unidirectional, i.e. endometriotic lesions simply just promote innervations. Rather, it is bidirectional, i.e. endometriotic lesions and nerve fibers engage active cross-talks, resulting in the development of endometriosis and pain. That is, nerve fibers and endometriotic lesions are actually partners in crime in inflicting pains in women with endometriosis, aided and abetted possibly by other culprits, some yet to be identified. We provide a list of possible perpetrators likely to be involved in this crime. Finally, we discuss some possible implications when viewing the relationship from this vista. Due to space limitations, we shall not delve into possible pain pathways involved in EAP.

A primer on nerve fibers

The perception of pain is mediated by a crosstalk between the CNS and the peripheral nervous system (PNS) that is exerted by afferent and efferent nerves. Sensory nerves belong to afferent nerves that carry nerve impulses from peripheral receptors toward the CNS. Based on their sizes, peripheral nerve fibers can be classified as three types [22] (Table 1). These sensory nerves include chemo-, mechano-, photo-, and thermo-receptors, as well as nociceptors. Thousands of afferent neuronal cell bodies are aggregated in a swelling just outside the spinal cord known as the dorsal root ganglion (DRG).

The efferent nervous system includes the motor nerves and the autonomic nerves involved in the function of internal organs. The autonomic nervous system (ANS) is comprised of two branches, the sympathetic and the parasympathetic nerves. Depending on the neurotransmitters released from the axon terminals, the efferent nervous system can be further divided into cholinergic and adrenergic nerves. The former, which include all preganglionic fibers and parasympathetic postganglionic fibers, release acetylcholine (ACh) while the latter, which include almost all of sympathetic postganglionic fibers, are specialized to release norepinephrine (NE) [23,24] (Fig. 1).

Neural density and neural remodeling in endometriosis and adenomyosis

The earlier attempts in the late 1990s to find the anomaly, if any, in nerve fibers in endometriosis were unfruitful [25,26]. In fact, an earlier study found no nerve fiber in endometriomas [27]. However, Anaf's group was the first to report possible involvement of nerve fibers in the EAP [28]. Based on the observation that uteri from patients with chronic pelvic pain showed proliferation of small-diameter nerve fibers throughout the myometrium [29], Quinn postulated that nerve injury (denervation) in uterus and/or uterosacral ligaments, due to either difficult intrapartum episodes in parous women or persistent straining to achieve defecation in nulliparous women, followed by re-innervation in the uterine isthmus may be the primary source of many clinical symptoms, and retrograde menstruation with adhesion of endometrium to injured tissue surfaces may lead to endometriosis [30–32].

Firm evidence for hyperinnervation in endometriotic lesions came from animal experimentation performed by neurobiologist Berkley's group [33,34], which was soon confirmed in human endometriosis [35]. The interest in nerve fibers was catapulted to a new height when Fraser and his associates published a series of studies showing the presence of nerve fibers in endometrium from women with endometriosis but the complete absence in women without, and reported an unprecedented 100% sensitivity and 100% specificity in classifying patients based on the presence of nerve fibers in endometrium [36–42]. Challenges in differential diagnosis aside, the rosy prospect of a novel, minimally invasive diagnostic biomarker with perfect sensitivity and specificity generated a great deal of excitement, prompting many investigations in this field.

Given the nature of chronic, visceral pain in endometriosis, the great majority of endometrial nerve fibers are reported to be unmyelinated C fibers, while myelinated Aδ fibers may also be involved [43]. An array of specific neural markers, such as protein gene product 9.5 (PGP9.5), substance P (SP), calcitonin gene-related peptide (CGRP), and tyrosine hydroxylase (TH) have been reported to be stained positive in nerve fibers in or surround endometriotic lesions of different types, and the consensus is that there is hyperinnervation in both ectopic and eutopic endometrium from women with endometriosis [28,34,35,38,39,44–63] (Table 2). Compared with other pelvic lesions, deep infiltrating endometriosis (DIE) seems to present a higher density of nerve fibers [64]. Adenomyosis, once considered to be endometriosis *interna*, appears to be different from endometriosis, in that both the functional layers and myometrium of women with adenomyosis had a tendency to show fewer nerve fibers compared with women without [44,52,65].

Table 1
Different types of peripheral nerve fibers.

Type of fibers		Function	Axonal diameter (μm)	Conduction velocity (m/s)	Direction of conduction
A (myelinated)	α	Proprioception, muscle contraction	12–22	70–120	Afferent and efferent
	β	Touch-pressure, vibration	6–12	80	Afferent and efferent
	γ	Intrafusal fibers contraction	4–8	15–30	Efferent
	δ	Pain (acute, shallow), temperature (cold receptors), touch-pressure	1–5	4–30	Afferent
B (myelinated)		Preganglionic fibers of ANS	1–3	3–15	Efferent
C (unmyelinated)	Fibers of dorsal roots	Pain (chronic, deep), temperature (warmth receptors), touch-pressure (tactile or mechanoreceptors)	0.2–1.5	0.5–2	Afferent
		Postganglionic fibers of sympathetic nerves	0.2–1.5	0.5–2	Efferent

Source: Compiled from Refs. [22,23].
ANS: autonomic nervous system.

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