

A life of pelvic pain

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Abstract

Pelvic pain associated with menstruation, i.e., dysmenorrhea, is a chronic pelvic pain that not only interferes with a woman's wellbeing for a large part of her life but also often co-occurs with other chronic painful conditions such as interstitial cystitis and irritable bowel syndrome and others. Little has been known about mechanisms underlying these chronic pelvic pains. This paper reviews 37 years of research in my laboratory at Florida State University on such mechanisms. Our research, mostly on rats, has contributed to the following findings: (1) Female reproductive organs are innervated in a topographic fashion by afferents in the pelvic (vagina/cervix) and hypogastric (cervix/uterine horn) nerves. (2) The input contributes to uterine and vaginal perceptions (nociception) that are modified by reproductive status. (3) Throughout the CNS, neurons responsive to stimulation of the reproductive tract also respond to stimulation of skin and other internal organs, in a manner modifiable by reproductive status and peripheral pathophysiology. (4) This dynamic physiological convergence may reflect extensive anatomical divergence of and interconnections between pathways entering the CNS via gateways through the spinal cord, dorsal column nuclei, and solitary nucleus. (5) The convergence also indicates the existence of extensive cross-system, viscerovisceral interactions within the CNS, that, while organized for coherent bodily functioning, serves as a substrate by which pathophysiology in one organ can influence physiology and responses to pathophysiology in other organs. (6) Some cross-system effects observed so far include: (a) Bladder inflammation reduces the rate of uterine contractions and the effects of drugs on the uterus. (b) Colon inflammation produces signs of inflammation in the otherwise healthy bladder and uterus. (c) A surgical model of endometriosis produces vaginal hyperalgesia, exacerbates pain behaviors induced by a ureteral stone, and reduces volume voiding thresholds if the bladder. These cross-system effects, which likely involve CNS mechanisms, likely also underlie co-occurrence of painful clinical conditions. Research continues on details of these mechanisms and their relevance for clinical diagnosis and therapy. None of this work could have been done without collegial support of colleagues and technical staff at Florida State University.

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1. Introduction

Dysmenorrhea, which is recurrent menstrual pain, affects a majority of women of reproductive age, often with a severity that reduces quality of life [39,67]. Furthermore, severe dysmenorrhea often co-occurs with other chronic painful conditions, such as interstitial cystitis, irritable bowel syndrome, fibromyalgia, headache, temporomandibular disorder, and chronic fatigue syndrome [1].

From a Darwinian perspective this fact seems curious. Why should menstruation, a healthy component of reproductive physiology, be painful and co-occur with so many other chronic pain conditions? Such questions have puzzled me since 1955, when, simultaneously, I learned about evolution and began experiencing severe, disabling dysmenorrhea.

Thus, at age 13, I began a life-long quest to satisfy curiosity in a manner that I hoped would have clinical meaning. Still unknown today is why menstruation is so often painful. Perhaps we will never know the answer: Can science ever reveal *why* anything happens? On the other hand, the process of trying to understand both *how*

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dysmenorrhea occurs and the consequences of its occurrence has provided many continuing joys of discovery, virtually all of them during my 38 years in the nurturing environment of the Neuroscience Program (previously Psychobiology Program) at Florida State University (FSU). Here I will describe the history, rationale and strategies for some of these studies, their results, their significance, and what may be next.

2. The pain pathway concept of pain

When I began research at FSU in 1967, it seemed self-evident that pain, being such a fundamental dynamic perceptual and motivating experience, was a creation of an individual's central nervous system. On the basis of clinical evidence, the “spinothalamic tract,” which consisted of fibers in the anterolateral quadrant of the spinal cord that relayed information from spinal recipient neurons to the thalamus, was then commonly considered the “pain pathway” [51]. It was soon found that fiber systems descending from brain to the spinal cord could modify the input at its entry “gate,” a process that helped explain how pain could vary in different circumstances [3,49]. This pain pathway was usually contrasted with the “touch pathway,” which consisted of primary afferent fibers in the dorsal columns relaying tactile information to the gateway of the dorsal column nuclei and thence to the thalamus and cerebral cortex. Another “pathway” involving the solitary nucleus as its gateway was organized to deal with internal organs (reviewed in [16]). Thus, the contemporary conceptualization consisted of modifiable channels or pathways of perceptual qualities gated at the

spinal cord, dorsal column nuclei and solitary nucleus [68] (Fig. 1A).

3. Divergent and convergent anatomic connectivity of the somatosensory systems

My graduate research had assessed how the thalamus in primates was involved in “pain and fear,” but its results did not easily fit the concept described above; too many parts of the thalamus seemed involved in both functions [15]. Because of this difficulty, I started research at FSU by using the then newly developed anatomical tracing techniques to study wiring patterns of these pathways in primates and cats in more detail.

It soon became evident that the pathway conceptualization was too simple. First, in primates, it was already known that meagre numbers of ascending spinal fibers actually arrived in the thalamus (<10%) [47,48]. Furthermore, a series of studies began to show that anterolateral quadrant fibers diverged, conveying their spinally-processed information not only to several parts of the thalamus, but also to many other parts of the brainstem and the cerebellum [17,48]. The same situation applied for output from the dorsal column and solitary nuclei (e.g., [8,16] and Fig. 2A). Furthermore interconnections between systems were extensive not only between the three gateways (e.g., reciprocal interactions between spinal cord and the dorsal column and solitary nuclei [7,43]) but also for the recipient regions further rostrally (e.g., [21]).

An obvious outcome of such extensive divergence and interconnectivity is, of course, convergence. And, indeed neurons in somatosensory brain areas were soon shown to

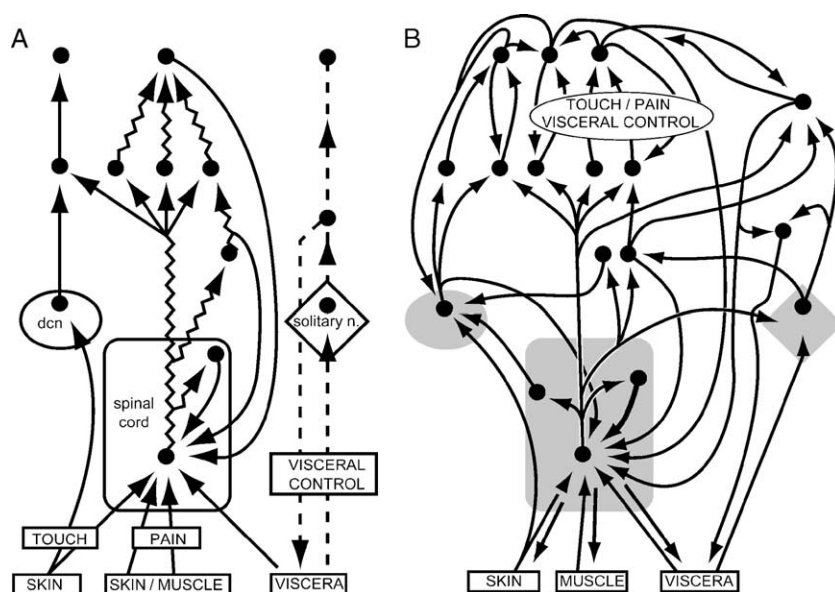


Fig. 1. Conceptualizations of perceptual mechanisms of touch and pain. Redrawn and modified from Ref. [11]. See text for further details.

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