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Pain classics: Special review

Constructing and deconstructing the gate theory of pain

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ABSTRACT

The gate theory of pain, published by Ronald Melzack and Patrick Wall in *Science* in 1965, was formulated to provide a mechanism for coding the nociceptive component of cutaneous sensory input. The theory dealt explicitly with the apparent conflict in the 1960s between the paucity of sensory neurons that responded selectively to intense stimuli and the well-established finding that stimulation of the small fibers in peripheral nerves is required for the stimulus to be described as painful. It incorporated recently discovered mechanisms of presynaptic control of synaptic transmission from large and small sensory afferents, which was suggested to "gate" incoming information depending on the balance between these inputs. Other important features included the convergence of small and large sensory inputs on spinal neurons that transmitted the sensory information to the forebrain as well as the ability of descending control pathways to affect the biasing established by the gate. The clarity of the model and its description gave this article immediate visibility, with numerous attempts made to test its various predictions. Although subsequent experiments and clinical findings have made clear that the model is not correct in detail, the general ideas put forth in the article and the experiments they prompted in both animals and patients have transformed our understanding of pain mechanisms.

1. Introduction

It is approaching the 50th year since the landmark article advancing the gate theory of pain was published [45]. Although this article is only one of many influential articles in the pain field, it holds a special place because of its clear theoretical position on how pain is coded and its elaboration of a specific model to achieve this based on then available electrophysiological evidence. Given its prominence, it is valuable to review the findings that led up to its publication. Because Melzack and Wall provided such a clear statement about pain mechanisms, many of the subsequent developments in the field were evaluated with reference to the gate theory, and so a discussion of this article can provide a window into the history of the field at that time and subsequently. The article made certain predictions that have been influential in the pain field and beyond. Other conclusions made using available experimental data turned out to be incorrect. A full evaluation of the gate theory requires discussion of both its successes and its failures; in so doing, a more complete perspective is provided as to its role in the development of modern pain theory.

Early work based largely on lesions and electrical stimulation of peripheral nerves had provided an outline of what could be called a pain pathway projecting from the periphery to the cortex by way of the spinal cord, brain stem, and thalamus. Despite this basic information, it was not possible to permanently abolish pain in patients surgically or pharmacologically. Beginning with a series of articles by Ronald Melzack, joined later by Patrick Wall, a new conceptual framework for pain was advanced. This framework drew on provocative behavioral observations with important implications for pain mechanisms. Later work made use of new experimental evidence illuminating processing of sensory input in the spinal cord. This led to a simple, elegant mechanism for pain coding that stimulated new modalities of treatment for certain painful conditions. This mechanism, called the gate, provoked a number of important experiments which advanced the study of pain without necessarily confirming the gate mechanism.

2. Early studies

Modern studies leading to the gate theory hypothesis began with the work of Ronald Melzack, a student of D.O. Hebb at McGill. He noted that dogs maintained in a restricted sensory environment would bump their head on exposed pipes when allowed to run freely and would not avoid these obstacles subsequently. This observation prompted a formal study of the effect of experience on the reaction to stimuli normally causing pain in dogs beginning at 4 weeks of age. The deficit was not in the ability to react immediately to the intense stimuli but rather in the subsequent avoidance behavior. The important conclusion was stated as

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follows [42]: "The results which have been reported here then, make it difficult to treat behavior related to pain simply in terms of frequency and intensity of stimulations or in terms of imperative reflex responses alone without regard to the earlier perceptual experience of the organism." This conclusion differs substantially from earlier ideas about pain, notably the iconic picture from Descartes suggesting that pain was an obligatory response to stimulation of elements responsive to the intense stimulus. As he stated, "If ... fire comes near the foot, the minute particles of this fire ... set in motion the spot of the skin of the foot which they touch, and ... pulling on the delicate thread ... they open up at the same instant the pore against which the delicate thread ends, just as by pulling at one end of a rope one makes to strike at the same instant a bell which hangs at the other end" [45]. Apart from details about sensory transduction and axonal conduction, this formulation is identical to what we would now call the labeled line mechanism for pain.

In the early 1960s, Melzack, now at MIT, began collaborating with Patrick Wall, whose spinal cord physiology laboratory had been there since the mid-1950s. Their first joint effort was a theoretical article discussing sensory physiology, including pain processing [44]. From his previous work, Melzack was already disposed toward the idea that sensory circuits were not labeled lines such that activation of a particular receptor resulted in a particular sensation, such as touch receptor/touch or pain receptor/pain. Wall had similar ideas based on his work on modification of sensory input at the first spinal synapse due to presynaptic inhibition [24,64]. They noted the ongoing controversy about cutaneous sensory mechanisms, with one opinion originating with von Frey that cutaneous modalities were fixed beginning with anatomically distinct cutaneous receptors responsible for different modalities—touch, warm, cold, and pain. The other view was championed by Weddell, Sinclair, and others on the basis of a lack of correspondence between anatomy and adequate stimulus of receptors. They suggested that stimulus modality was signaled by the spatiotemporal barrage of impulses in sensory fibers. (See the discussion in [44] for a review of these concepts.)

Melzack and Wall deconstructed von Frey's theory of specificity into 3 assumptions: Although they accepted the possibility that individual receptors might have a specific anatomy (the anatomical assumption) correlated with sensitivity to a specific physical stimulus (the physiological assumption), they were skeptical that the "psychological dimension of the somesthetic experience" could be identified with a specific skin receptor type (the psychological assumption). They argued in favor of a pattern theory where barrages of impulses produced in different sensory fibers initiated a computation in the central nervous system that was decoded into a somesthetic experience based in part on other ongoing brain activity. A corollary was the possibility that interference with the barrage or with the computation of its effects might prevent accurate interpretation, as for example the inability of experience-deprived dogs to react appropriately to intense stimuli.

In this article, Melzack and Wall drew special attention to Goldscheider's original proposal reemphasized by Livingston [11,35] that central summation is important for generating impulse patterns interpreted as pain. They cited the lack of evidence for individual sensory fibers responding selectively to intense, presumptively painful stimuli. They suggested that pain might arise only when the number of responding fibers as well as their frequency of discharge exceeded some threshold.

3. Inhibition of cutaneous input to the spinal cord

Two major advances in the late 1950s were very influential in the development of the gate theory. The first was a clinical finding from analysis of patients with herpes zoster. These patients experience excruciating pain in response to gentle stimulation of the affected area. Noordenbos [56] showed that the fraction of large fibers in nerves innervating these areas was diminished. He suggested that large fibers normally inhibit the effects of small fibers, and that this inhibition is reduced in the diseased nerves. This led to the idea, so important in the formulation of the gate theory, that the balance between the large and small fiber input was a major factor in determining the painfulness of a stimulus.

A second advance began with the seminal work of Frank and Fuortes [18], who demonstrated long-lasting presynaptic inhibition of input to motor neurons elicited by volleys in large afferent fibers. Later, both Wall [65] and Eccles et al. [16] both demonstrated that the central effects of volleys in cutaneous afferent fibers were presynaptically inhibited by conditioning volleys in other segmentally close cutaneous afferents. Up to this point, studies of synaptic effects had been largely restricted to the effects of large-diameter myelinated afferent fibers. Mendell and Wall [50] investigated the presynaptic effects of activity in small-diameter unmyelinated afferent fibers. These were of interest because electrical stimulation of peripheral nerves in human subjects had shown that stimulus intensities high enough to activate unmyelinated fibers were required to elicit pain [9]. Mendell and Wall measured the presynaptic effect of small fiber stimulation by measuring the dorsal root potential (DRP) and by testing the excitability of the terminals of sensory fibers. Presynaptic inhibition is signaled as a negative DRP associated with depolarization of the fiber terminals and as an increase in electrical excitability of the depolarized terminals (reviewed in [57]). When unmyelinated fiber volleys were elicited in isolation using direct current anodal block to prevent conduction in the concomitantly activated large-diameter afferents, the DRP was reversed in sign (Fig. 1), and the test of terminal excitability revealed a decline. Both of these were indicative of hyperpolarization of the terminals. This was interpreted as presynaptic facilitation.

The requirement to block inputs from large cutaneous Aβ fibers was due to the interference from the large negative DRPs they evoke. This was a technical limitation in these experiments that caused some controversy [76]. In later experiments where muscle nerves were activated, the positive DRP could be unambiguously observed in response to small fiber stimulation without the need for large fiber blockade because large proprioceptive afferent fibers evoke much smaller negative DRPs than large cutaneous afferent fibers [47].

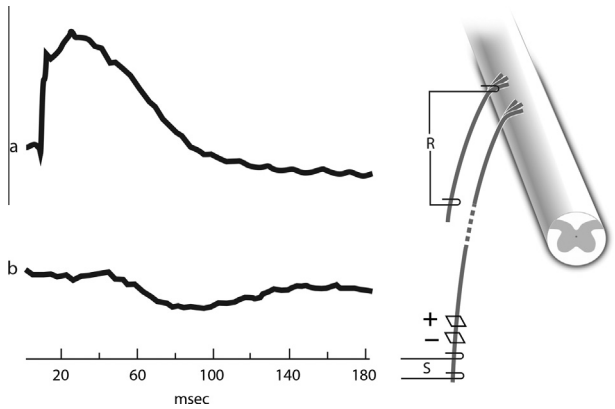

Fig. 1. Negative (upward-going) and positive (downward-going) dorsal root potentials produced by stimulating large (A-) and small (C-) fibers. The diagram illustrates the dorsal root potential recording (R) and sural nerve stimulation (S). The square electrodes (+ and −) on the peripheral nerve illustrate the arrangement to produce selective anodal block of the large A-fibers that permitted the effects of C-fibers to be observed selectively (from [50] with permission).