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·Review·

History of pain theories

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Abstract: The concept of pain has remained a topic of long debate since its emergence in ancient times. The initial ideas of pain were formulated in both the East and the West before 1800. Since 1800, due to the development of experimental sciences, different theories of pain have emerged and become central topics of debate. However, the existing theories of pain may be appropriate for the interpretation of some aspects of pain, but are not yet comprehensive. The history of pain problems is as long as that of human beings; however, the understanding of pain mechanisms is still far from sufficient. Thus, intensive research is required. This historical review mainly focuses on the development of pain theories and the fundamental discoveries in this field. Other historical events associated with pain therapies and remedies are beyond the scope of this review.

Keywords: pain; theory; history

1 Before 1800

In oriental medicine or traditional Chinese medicine (TCM), the term for pain appeared for the first time in the ancient medical book *Huang Di Nei Jing* more than 3 000 years ago, which was translated into English as *The Yellow Emperor's Classic of Internal Medicine* by Veith in 1966[1] and *The Medical Classic of the Yellow Emperor* by Zhu in 2001[2]. In this TCM canon, pain was believed to be a result of imbalance between *yin* and *yang*. Predominance of *yin* results in '*han'* (cold), causing damage to the '*xing*' (form of a substance) which is now known as tissue injury or damage, and leads to swelling, while predominance of *yang* results in '*re*' (hyperthermia or heat) which causes damage to the '*qi*', namely pneuma (previously referred to as '*chi*', the concept of energy circulating in the hypothetical 12 channels), and leads to pain. That was probably the first description of the symptoms and signs of nociceptive and inflammatory pain in the medical literature. Based upon this principle, any TCM treatment of pain, regardless of pharmacological or non-pharmacological approaches, has focused on restoration of the balance between *yin* and *yang*, including the use of acupuncture analgesia.

In Western countries, the description of pain appeared for the first time in Homer's epics, *the Iliad* and *the Odyssey*, from around the 8th century BC in ancient Greece[3]. The term for pain appearing in the literature of Occidental medicine can be traced back to the Hippocratic period (5th century BC) when he and his followers published *the Hippocratic Collection*[3]. However, the brain was not believed to be the seat of pain sensation until the Renaissance (14th–17th centuries) when systematic autopsies were

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carried out by Andreas Vesalius (1514–1564), the founder of modern human anatomy, who published the classical book on the subject, *On the Fabric of the Human Body*[3-5]. Before the Renaissance, according to Aristotle's postulate, the heart was considered the seat of sensations (hearing, vision, smell, taste, and pain), emotions and mental functions. Actually, the idea that the brain was the seat of perception had been postulated by a few philosophers and physicians, such as Pythagoras (570–495 BC), Anaxagoras (500–428 BC), and Galen (130–201) in ancient times, and Avicenna (980–1037) in the middle ages[3-5]. Galen recognized the brain as the site of feeling. By carefully observing patients suffering from various pain problems, he proposed that pain is a specific characteristic of the tactile sensation which corresponds to the phenomenon of allodynia (now referred to as a painful sensation caused by a previously non-painful stimulus in a pathological state). Galen also described inflammation as characterized by pain (dolor), heat (calor), redness (rubor), and swelling (tumor). In China, Hua Tuo (145–208), an ancient Chinese physician, administered a herbal concoction called '*mafeisan*' (the ingredients were cannabis in wine), to patients receiving surgery. He was probably the first Chinese physician to introduce the concept of anesthesia and analgesia in the history of TCM. Avicenna, a renowned Muslim philosopher and physician, proposed for the first time that pain is an independent sensation that is dissociated from touch or temperature, in his work *Canon of Medicine and Poem of Medicine*[5,6]. Avicenna has been regarded as the first man to formulate the specificity theory[6].

In the 17th century, the functions of the brain were significantly promoted by René Descartes (1596–1650), Thomas Willis (1621–1675), and Thomas Sydenham (1624–1689)[3,5]. Descartes, a French writer and 'Father of Modern Philosophy', provided a famous hypothetical drawing that showed the transmission of pain information via the peripheral nerves and the spinal cord to the ventricles of the brain and the pineal organ where the conscious perception of a painful stimulus was proposed to be produced. Thomas Willis, recognized as the discoverer of the 'circle of Willis', was a pioneer of brain anatomy. In his work *Cerebri Anatome* (1664), he provided strong evidence supporting the roles of the brain (including the cerebral cortex), but not the ventricles, in the perception of pain[3]. Thomas Sydenham was the first to use laudanum, a composite of opium, saffron, cinnamon, and cloves in wine, and promoted the consistent and systematic treatment of pain[5]. He was also the first physician to describe gout, a disease he had himself.

2 After 1800

The concept of pain has been gradually shaped due to the development of experimental sciences since 1800. However, the ideas about pain have long been debated due to the complexity of pain itself and the brain, the generator of pain[6]. The main dispute is whether pain is mediated by a specific, hard-wired pathway or a non-specific pathway in the nervous system. So far, 4 theories of pain have been proposed: specificity theory, intensity theory, pattern theory, and gate control theory, none of which has been generally accepted to be exclusively correct (Fig. 1).

The specificity theory (Fig. 1A) was one of the most influential theories of pain in history. In 1811, Charles Bell (1774–1842), a Scottish physician and anatomist, described in his privately circulated book, *An Idea of a New Anatomy of the Brain*, that the dorsal and ventral roots of the spinal nerves serve different functions[4,6]. However, he emphasized the involvement of the ventral roots in control of muscle contraction, but without a clear description of the functions of the dorsal roots. Eleven years later in 1822, François Magendie (1783–1855), a French physiologist, verified the sensory characteristic of the dorsal root nerves[4,6]. There was a continuous dispute and rivalry between them because each insisted that he was the first discoverer. This was finally referred to as the Bell-Magendie law, stating that the anterior branches of spinal nerve roots contain only motor fibers and that the posterior roots contain only sensory fibers. These discoveries provided a fundamental basis for the scientific study of pain issues. Based largely on this law, the German physiologist Johannes P. Müller (1801–1858) developed the concept of sensory nerve specificity, the "law of specific nerve energies",

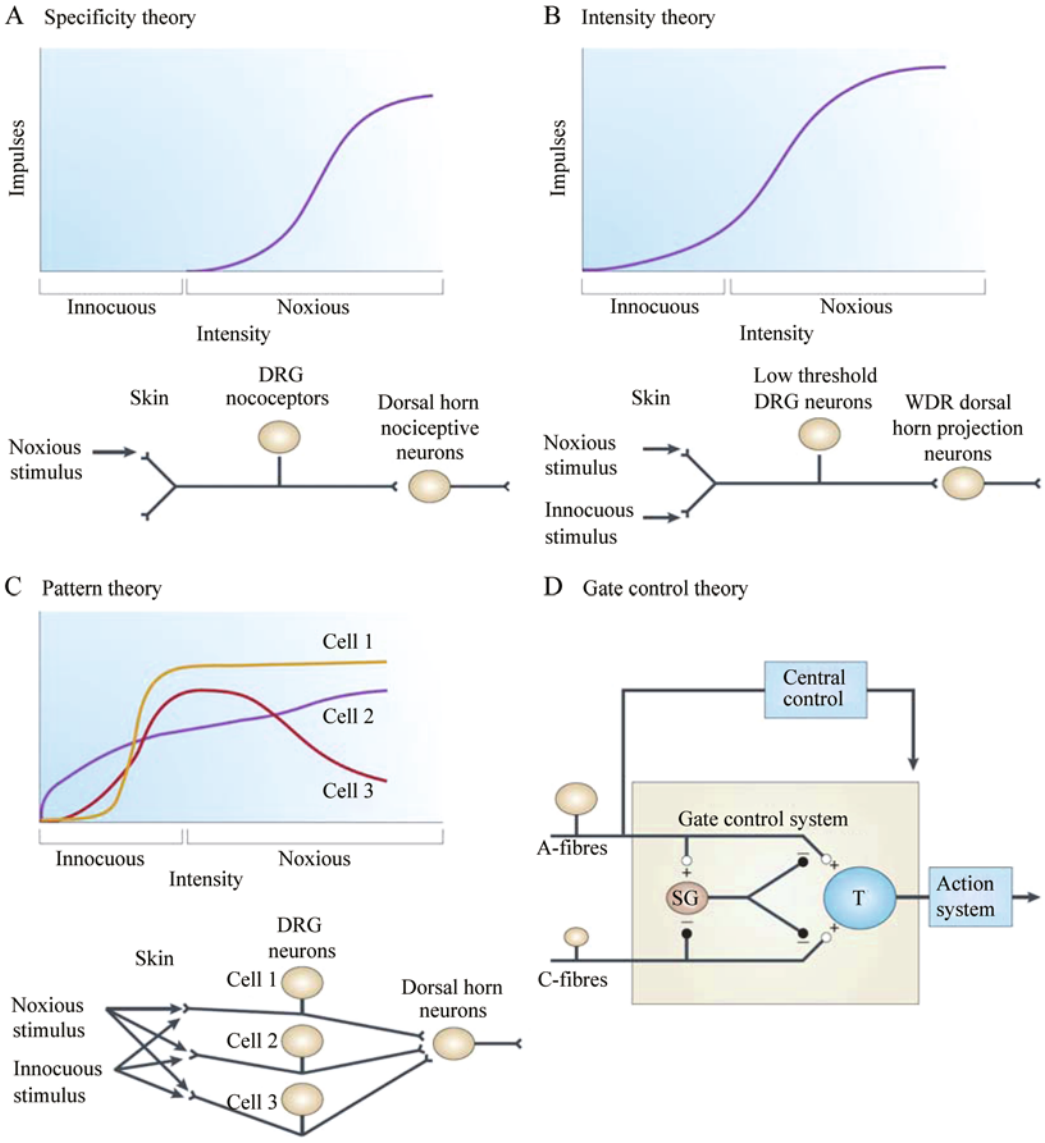

Fig. 1 Theories of pain. Diagrams depicting typical assumptions about relationships between stimuli and primary afferent signalling in theories about pain (adopted from Perl ER, 2007[6] with permission from Nature Publishing Group). A, According to the specificity theory, specialized sense organs (nociceptors) have thresholds at or near noxious levels, increasing activity with stronger noxious stimuli. These special peripheral afferent neurons have selective connections to particular spinal and brainstem projection neurons. B, The intensity theory suggests that peripheral sense organs are not differentiated into low- and high-threshold types. It proposes that afferent fibers transduce innocuous stimuli (for example, skin pressure) by generating a certain level of activity, whereas noxious stimuli are signaled by a greater level of discharge. The intensity-coded primary afferent fibers, in turn, activate projection neurons with a wide dynamic range (WDR). Weak activation of WDR projections indicates innocuous stimuli; strong activation indicates painful (noxious) events. C, The pattern theory proposes that somatic sense organs have an extensive range of responsiveness. Individual afferent neurons respond to stimuli with differing relationships to intensity. The mode and the locus of stimulation are indicated by the composite pattern of activity in the population of fibers from a particular body region. Central projection neurons code the nature and place of stimulation by the pattern and distribution of their discharges. D, According to gate control theory, the spectrum of primary afferent neurons has a range of thresholds, specialized nociceptors and dedicated central pathways do not exist, and large-diameter primary afferent fibers (A-fibers) adapt more quickly to maintained stimuli than thin ones (C-fibers). A presynaptic gate in the substantia gelatinosa (SG) of the spinal dorsal horn between primary afferent and projection neurons is controlled by the balance of activity between the A-fibers and the C-fibers. When the C-fiber input outweighs that of the A-fibers, the gate opens, permitting activation of projection neurons. CNS mechanisms (descending control) are postulated to modulate the gate. DRG, dorsal root ganglion; T, transmission neurons.

which had a long-time influence on theories of pain[4]. The specificity theory was further refined by Moritz Schiff (1823–1896), Magendie's student, who demonstrated, by his experiments in dogs in 1849, that the pathway conveying information about temperature and pain differ from that of other sensations such as touch, cross in the spinal cord, and do not ascend in the dorsal columns[3,4,6]. Schiff's proposal was confirmed by his contemporary Charles-Edouard Brown-Séquard (1817–1894), who published a series of results from animals and human cases with loss of pain and temperature sensibility contralateral and distal to a transverse hemisection of the spinal cord (Brown-Séquard syndrome or hemiplegia) in the 1860s[4,6]. The dissociation of ascending pathways mediating pain and touch in the spinal cord was also more extensively confirmed by both basic anatomical research in animals by L. Edinger and clinical cases reported by Sir William Gower (1845–1915) in 1878 and William Gibson Spiller (1863–1940) in 1905[4,6]. As an example of 'proof of concept', Spiller and Edward Martin (1859–1938) published their first clinical result in 1912 in which good relief of pain was achieved in one of their patients by cutting the anterolateral quadrants of the spinal cord[4,6]. In 1884, Magnus Blix (1849–1904) and Adolf Goldscheider (1858–1935) demonstrated the mosaic of skin sensation and pain spots[4,6]. During 1894–1897, Max von Frey (1852–1932) further provided evidence linking specific sensory nerve endings in the skin to the sensation of pain[4,6]. Sir Charles Scott Sherrington (1857–1952), the Nobel laureate in Physiology or Medicine in 1932, introduced the concept of nociception in 1906 which emphasized tissue injury as a common source of pain[4,6]. The introduction of the concept of nociception is of particular importance. On one hand, it set up a common stage for debate regardless of which pain theory is correct. On the other hand, Sherrington also provided an experimental model of the spinal nociceptive flexion reflex as a surrogate for pain sensation which has been widely used in the field of pain research ever since. In his book, *The Integrative Action of the Nervous System*, he also proposed the concept of the synapse, which led to the anatomical discovery of pre- and post-synaptic components and the discovery of synaptic transmission and modulation in the central nervous system (CNS), a principle of brain structure and functions.

Before the introduction of the nociception concept, the specificity theory was mostly supported by physiologists and some physicians but not by psychologists. In 1874, the German neurologist W. Erb proposed the intensity theory of pain, which, instead of considering the existence of specific organs in the body, claimed that pain was produced by stronger activation of nerves by an intense stimulus, while a weak stimulus produced non-painful sensation (Fig. 1B)[6]. The discovery of wide-dynamic-range (WDR) neurons in the dorsal horn of the spinal cord and the stimulus-response characteristics of the visceral sensory system in the 20th century supported the intensity theory of pain.

The emergence of the pattern theory was mostly dependent upon the development of the cathode-ray oscilloscope (CRO) and the use of electrophysiological recordings to identify and classify single sensory afferent fibers according to size and conduction velocity by Joseph Erlanger (1874–1965) and Herbert Spencer Gasser (1888–1963), co-recipients of the Nobel Prize for Physiology or Medicine in 1944, and other electrophysiologists[4,6]. Anatomically, the primary afferent fibers have been classified into myelinated and unmyelinated fibers. Based on the conduction velocities, Aα and Aβ are rapidly-conducting, thickly-myelinated fibers, while Aδ fibers are slowly-conducting, thinly-myelinated fibers. C fibers are the most slowly-conducting, unmyelinated fibers. At the very beginning of the 20th century, some researchers proposed that there are 2 different classes of somatic sensory pathways subserving epicritic or discriminating sensations (e.g. touch and pressure) and crude or protopathic sensations (e.g. pain)[7]. Later, S.W. Ranson (1915) proposed that fine, unmyelinated nerve fibers were conductors of protopathic sensation[8]. Clearly, these proposals favored the specificity theory. However, galvanometer recordings of the action potentials in the mid-1920s by Sir Edgar Douglas Adrian (1889–1977), co-recipient of the Nobel Prize for Physiology or Medicine in 1932 with Sir Charles Sherrington, and CRO-aided electrophysiological recordings by Erlanger,

Gasser and their collaborators, identified different patterns of neural activity from primary afferent nerve fibers in response to different stimulus modalities (mechanical, thermal and chemical)[6]. These findings led to the formulation of the pattern theory proposed by John Paul Nafe, an American psychologist, in 1929 (Fig. 1C)[9]. The pattern theory was developed into the gate control theory by Ronald Melzack and Patrick D. Wall in 1965 (Fig. 1D)[10], which prevailed and directed the development of pain research all over the world in the following 45 years, although it was recently argued to be too simple to explain pain mechanisms[6,11].

The gate control theory[10] proposes that there is a 'gating' at the first synaptic relay between primary afferents and transmission (T) cells (pain-signaling neurons) in lamina II (substantia gelatinosa, SG) of the spinal dorsal horn (Fig. 1D). The core of the theory has 3 facets. First, when the neural activity mediated by large (L) non-nociceptive afferent fibers prevails, it inhibits the activity of small (S) nociceptive afferent fibers via activation of inhibitory SG interneurons, resulting in hypoalgesia or analgesia. Second, when activity mediated by nociceptive afferent fibers prevails, it exacerbates pain via deactivation of the inhibitory SG interneurons. Third, the 'gating' is dynamically modulated by central control of descending or segmental origin. The flaws of the gate theory are clearly known today as suggested by Cervero[11]:

The main point of the theory was a restatement of pattern interpretations of pain mechanisms, which has been found, in the intervening years, to be a great simplification for the CNS or even plainly wrong for the organization of the peripheral input to the spinal cord. Other details of the theory regarding the dorsal horn organization of presynaptic links between A and C fibers have also been proven incorrect. However, the gate theory has had an overall positive effect in the field of pain research and has helped to draw attention to previously forgotten aspects of pain modulation.

Although development of the specificity theory waxed and waned before and after the introduction of the gate control theory, it has continued to survive. Actually, between 1930 and 1965, some electrophysiologists identified a class of thinly-myelinated and unmyelinated fibers that could be selectively activated by stronger stimuli[12-15]. The major reason for its failure to have a wide influence was probably that single C fiber recordings were too difficult to be widely carried out due to technical limitations, and the results from the small number of labs were not consistent. However, this situation was greatly changed by a series of publications from Edward R. Perl's lab since 1967[6]. Perl and his collaborators, using a modified single fiber recording technique, reliably identified a class of nociceptors innervated by either thinly myelinated or unmyelinated fibers in the cutaneous nerves of cats and monkeys[16-19]. These discoveries of nociceptors in animals were soon confirmed by Torebjörk and his collaborators in conscious human subjects using psychophysical microneurography[20-23].

They verified that pain sensation could only be evoked by activation of nociceptors, and not by low-threshold mechanoreceptors. Three years after they discovered nociceptor fibers in the periphery, Perl and his collaborator Christensen[24] further identified a class of central neurons referred to as nociceptive-specific (NS) neurons within lamina I of the spinal dorsal horn. This class can only be activated by noxious stimuli, differing significantly from the characteristics of WDR neurons. NS neurons have been identified in the ventrobasal complex of the thalamus and the primary somatosensory cortex since the mid-1980s. Moreover, neurochemical studies provided another line of evidence showing the localization of neuropeptides (e.g. substance P and calcitonin gene-related peptide) in a small population of dorsal root ganglia (or trigeminal ganglia) cells innervating thinly-myelinated and unmyelinated fibers that project their central terminals mainly to the superficial layers of the dorsal horn[25,26]. According to the neurochemical properties and central projections of the primary afferent fibers, nociceptors are generally accepted to be divided into 2 classes, peptidergic and non-peptidergic[27]. TRPV1, a type of thermal nociceptor molecule and capsaicin receptor, was identified by D. Julius and his colleagues in 1997, and this is regarded as a landmark in the history of pain research for understanding the molecular and cellular mechanisms[28]. Although the discovery of nociceptors,

central NS neurons, and even nociceptor molecules further support the specificity theory, none of the existing theories explains everything. Pain has two faces and is state-dependent in terms of physiology and pathology. Pain is also a complex experience associated with multiple dimensions of brain function, including sensory discrimination, affective motivation, and cognitive evaluation, the mechanisms of which so far remain largely unknown.

In the history of pain, other profound events were the discoveries of the endogenous descending pain modulation system and opioid peptides as well as their receptors in the CNS. These have been regarded as cardinal for the gate theory because they, for the first time, clearly proposed central origins of pain modulation at the level of the spinal cord. Actually, however, one year before the publication of the gate theory, Tsou and Jang (1964)[29], neuropharmacologists in China, discovered that microinjection of morphine into the midbrain periaqueductal gray (PAG) resulted in powerful analgesia in rabbits, which led to a presumption of the existence of endogenous 'receptors' for morphine. Five years later (1969), Reynolds[30] discovered that electrical stimulation of the PAG also resulted in strong antinociception in rats receiving surgery. These 2 discoveries had a profound and fruitful influence upon the field of pain research, leading to a series of discoveries of μ-, δ-, and κ-opioid receptors and opioid peptides (such as enkephalin, endorphin, dynorphin and endomorphin) during the 1970s to 1990s[5]. Identification and characterization of the cellular and molecular properties of opioid receptors and their endogenous ligands in the CNS underlie the mechanisms of morphine-induced analgesia and brain stimulation-induced analgesia[5]. The discoveries associated with the endogenous opioid peptides and their receptors also provided an interpretation of acupuncture analgesia which has been shown to involve frequency-dependent release of endorphins and dynorphins at both the brain and the spinal cord levels[31]. The investigation of acupuncture analgesia in China was initiated by H.T. Chang (1907–2007), a renowned neurophysiologist, who with his colleagues coined the concept of thalamic integration as the underlying neural mechanisms of acupuncture analgesia[32]. It is now generally accepted that the neural circuits of the endogenous descending pain modulation system comprise the PAG-rostroventral medulla (RVM)-dorsal horn pathway[33]. Within the RVM, 2 types of cells have been identified: the On-cell, which is activated by painful stimulation, and the Off-cell, which is inhibited by painful stimulation but activated by morphine[34]. The balance between the states of these 2 types of RVM cells determines the pain control effect of opioids. However, in inflammatory and neuropathic pain states, the endogenous descending pain modulation system is changed due to RVM facilitation which exacerbates the pathological pain state[35,36]. Moreover, activation of the endogenous opioid system in the CNS has been demonstrated to be associated with placebo effects[37].

Pain is essential for human evolution by the force of natural selection because it serves as a sensory detection and alarm system for escape and survival when the body is hurt by harmful insults. It can also facilitate the healing of injuries. However, pain is harmful to health when it becomes persistent or chronic in a pathological state. Although the history of pain is as long as that of human beings, the understanding of pain mechanisms is far from sufficient. The existing theories of pain may be appropriate for the interpretation of some aspects of pain, but do not explain all. Thus, intensive research is required. The present historical review mainly focused on the development of pain theories and the fundamental discoveries in this field. The historical events concerning the development of pain therapies and remedies are beyond the scope of this brief introduction.

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疼痛学说发展史

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摘要：疼痛的概念是从古至今一直争论不休的话题。在进入19世纪之前，东西方医学界已有疼痛概念的雏形，但很肤浅。进入19世纪之后，由于实验科学的发展，持各种不同观点的疼痛学说应运而生，且逐步成为各家学说守护和争论的焦点。然而科学实践证明，每个学说可能在某些方面能够求证并释疑解惑，但都不是万能之说。疼痛问题本身的历史应该与人类诞生后的历史一样长，但是人类对疼痛机理的认识却令人惊奇地不足。因此，号召与倡导对疼痛问题的更深入研究是必要的。限于篇幅，此综述仅叙述疼痛学说的发展史和奠定该领域的基本科学发现，而不涉及疼痛治疗方法及对人类有益的镇痛名药良方的相关历史。

关键词：疼痛；学说；历史