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Review article

Research progress of mechanisms and drug therapy for neuropathic pain

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ABSTRACT

Neuropathic pain is maladaptive pain caused by injury or dysfunction in peripheral and central nervous system, and remains a worldwide thorny problem leading to decreases in physical and mental quality of people's life. Currently, drug therapy is the main treatment regimen for resolving pain, while effective drugs are still unmet in medical need, and commonly used drugs such as anticonvulsants and antidepressants often make patients experience adverse drug reactions like dizziness, somnolence, severe headache, and high blood pressure. Thus, in this review we overview the anatomical physiology, underlying mechanisms of neuropathic pain to provide a better understanding in the initiation, development, maintenance, and modulation of this pervasive disease, and inspire research in the unclear mechanisms as well as potential targets. Furthermore, we summarized the existing drug therapies and new compounds that have shown antalgic effects in laboratory studies to be helpful for rational regimens in clinical treatment and promotion in novel drug discovery.

1. Introduction

When noxious stimuli such as intense thermal, mechanical, and chemical stimuli are detected by the nervous system, acute pain is generated, rendering people conscious of the deleterious conditions, thus engaging appropriate behaviors to avoid being injured [1]. However, alterations of pain pathway elicited by tissue and nerve damage lead to hypersensitivity, characterized by spontaneous pain (no stimuli exist but the organism feels pain), allodynia (painless tactile stimulus or warmth are perceived as pain) and hyperalgesia (painful stimuli make the organism feel pain of greater intensity), such that pain does not serve as a warning signal and becomes chronic pain, making people suffer from persistent somatic disorders as well as psychological discomforts such as tension, anxiety and depression.

Neuropathic pain is a kind of chronic pain, defined by the International Association for the Study of Pain (IASP) as a pain arising after a lesion or disease affecting the somatosensory system [2]. Neuropathic pain refers to a wide range of symptoms like herpetic zoster neuralgia, diabetic neuralgia, trigeminal neuralgia in clinic. Because of the high incidence, complex pathogenesis and lack of efficient treatments, neuropathic pain is still the focus of many researches. Trauma (surgery, amputation), metabolic disorder (diabetes, uremia), infection (herpes zoster, HIV),

poisoning (chemotherapy), vascular disease (arteritis nodosa) and malnutrition are considered as elicitors for the initiation of peripheral neuropathic pain. By contrast, spinal cord injury, multiple sclerosis, and cancer are the main elicitors for the initiation of central neuropathic pain [3].

2. Anatomical physiology

2.1. Nociceptors and spinal dorsal horns

Nociceptors, a subpopulation of peripheral afferent nerve fibers, are the sensory neurons which can detect intense thermal, mechanical, or chemical stimuli that reach the “warning range”. The cell bodies of nociceptors generally reside in dorsal root ganglia (DRG) for the body and trigeminal ganglia for the face, with peripheral and central axonal branches, innervated the spinal cord and other target organs, respectively. Nociceptors can be divided into two major types: (1) Aδ and Aβ fibers; and C fibers (Table 1). Aδ fibers are medium diameter (1–5 μm) myelinated afferents that mediate acute pain with an exact location and a fast process for injury (first pain). Aδ fibers can be further subdivided into two types: high-heat-threshold (> 50 °C) type I and low-heat-threshold type II, and type II has a high mechanical threshold. Type I is considered as the detector that is more sensitive to mechanical and chemical stimuli (e.g. pinprick and chemical irritant), while type II generally responses to noxious heat. Different from Aδ fibers, Aβ fibers are larger diameter (6–12 μm) myelinated afferents that respond to innocuous stimuli such as light touch, and commonly associated with the experience of pleasure. The second type, C fibers, are small diameter (0.2–1.5 μm) unmyelinated fibers that detect both of thermal and mechanical stimuli, but compared with Aδ fibers, the pain procession is slow and the injured area is usually poorly located (second pain). Based

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Table 1
Pain related peripheral nociceptor.

Type	Subtype	Character	Function
A fibers	Aδ fibers(type I, type II)	Medium-diameter, myelinated	Detect noxious stimuli (first pain)
	Aβ fibers	Large-diameter, myelinated, Rapid-conduction	Detect innocuous stimuli
C fibers	Peptidergic C fibers	Small-diameter, unmyelinated, Slow-conduction	Release neuropeptide, SP, CGRP, etc. (second pain)
	Nonpeptidergic C fibers	Small-diameter, unmyelinated, Slow-conduction	Express c-Ret receptors, Mediate noxious stimuli Together with peptidergic C fibers

SP: substance P; CGRP: calcitonin-gene related peptide.

on the substances released, C fibers can be further subdivided into two subtypes: (1) peptidergic C fibers; and nonpeptidergic C fibers. Peptidergic C fibers release neuropeptide, substance P (SP) as well as calcitonin-gene related peptide (CGRP), expressing tropomyosin receptor kinase A (TrkA) receptors that bind to nerve growth factor [4], whereas nonpeptidergic C fibers are mainly associated with expression of non-peptide substance such as c-Ret neurotrophin receptors [1,5,6].

After the peripheral afferents (viz, nociceptors) detected the stimuli, pain messages convey to the central via the projection neurons in spinal dorsal horns, which is the origin of pain ascending pathways (Fig. 1. left). Gray matters of the spinal cord contain ten layers in total, wherein the laminae I to VI constitute the dorsal horns [7]. Laminae I, located in the superficial part of the dorsal horn, is adjacent to white matter and possesses the clearest sight of the lumbar enlargement, Laminae II resides in abundance of small neurons but rarely projected by myelinated fibers, thus myelin staining is useless to get this layer stained. Projection neurons in the laminae I and V serve as the dominating neurons for pain transmission from the dorsal horn to the brain, terminated on by afferent fibers most of that carry noxious inputs (C and Aδ fibers). Compared with Laminae II, laminae III is more projected to by myelinated fibers (Aβ fibers), and neurons in the laminae III have slightly larger cell body, smaller density as well as more diverse morphologies than that of neurons in the Laminae II. Laminae IV is thicker than other layers, where the loosely arrayed circular, triangle cells and astrocytes are in the majority, receiving innocuous stimulations together with Laminae III. Neurons in the laminae V receive both noxious and innocuous stimulations conducted by Aδ and Aβ fibers respectively. Laminae VI is basal in posterior horn of the spinal cord.

2.2. Ascending pathways and the cortex

Noxious stimulations detected by nociceptors are conducted to projection neurons mostly in the laminae I and V, and then pain messages reach the cerebral cortex through the thalamus or the amygdala, respectively (Fig. 1. right). The former transmits pain messages to the somatosensory cortex, where the location and intensity of pain can be determined, whereas the latter connects the parabrachial nucleus in the brainstem, and transmits pain messages to the cingulate cortex and insular cortex, which mainly deal with the emotional aspects of pain and the injured area is poorly located [8]. The cerebral cortex, the thalamus, and the limbic system are functionally linked with each other to process the pain sensation. As for pain modulation, the periaqueductal gray (PAG) and rostral ventral medulla (RVM) are the main structures in the descending pathways. Particularly, the PAG has been regarded as the core component for anti-nociceptive stimulation in the brain. Besides, connections between the anterior cingulate cortex (ACC), the amygdala and the PAG play an important role in the generation of reflex response to nociceptive stimuli [9].

2.3. Peripheral mechanisms of neuropathic pain

Various factors such as trauma, infection, and tumor infiltration contributed to nerve injury which triggers in ectopic discharge or

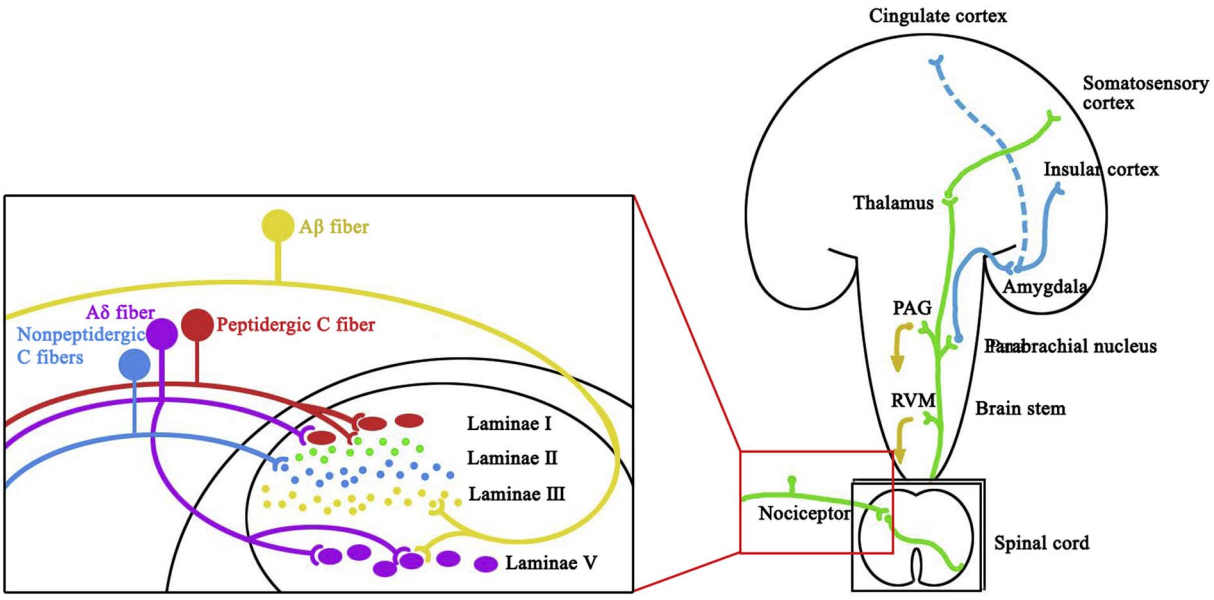

Fig. 1. Anatomy of pain pathway. (Left) The stratification of afferent fibers within the dorsal horn. C fibers (red and blue) project superficially to laminae I and II. Peptidergic C fibers terminate on neurons (red and green) located in the laminae I and II. Nonpeptidergic C fibers terminate on interneurons (blue) in the laminae II. Aβ fibers terminate on the excitatory interneurons (yellow) that express PKCγ (an isoform of protein kinase C, contributed to persistent pain procession) in the ventral half of the laminae II and neurons in the deep laminae III, IV, V. Aδ fibers terminate on neurons both in the superficial laminae I and deep laminae V. The physiological structures and pain procession. **Transduction:** the nociceptors detect the stimuli and conduct pain messages to the projection neurons in the spinal dorsal horn. **Transmission:** pain messages transmit to the cerebral cortex (somatosensory cortex, cingulate cortex, and insular cortex) via the ascending pathways (through the brainstem, PB, amygdala or the thalamus). **Interpretation:** the cerebral cortex handles the nociception and form pain sensation. **Modulation:** descending feedback system (including PAG and RVM) and various neurotransmitters indicated in the pain modulation leads to pain relief or hypersensitivity. PB: parabrachial nucleus; PAG: periaqueductal gray; RVM: rostral ventral medulla. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)