Chapter 7
Glial Cells Dysfunction and Chronic Pain

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ABSTRACT

Chronic pain is a pathological health condition caused by the imbalance between inhibitory and excitatory signaling pain pathways. This clinical problem affects about 30% of adults worldwide, and current treatments are insufficient with side effects. The mechanisms underlying this disease were thought to be a result of neuronal dysfunction, however, several animal studies clearly showed that non-neuronal cells (glial cells), primarily microglia and astrocytes, and their interaction with neurons, had a key role in pain persistence. A long-lasting state of activated glia turns to a pathological element causing a painful sensation. This chapter aims to elucidate glial dysfunction by shedding light on peripheral and central glial cells involved in the pathogenesis of chronic pain.

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INTRODUCTION

Chronic pain is a complex and debilitating condition that affects millions of people worldwide. It is characterized by persistent pain that lasts for weeks, months, or even years. It poses a substantial clinical challenge, impacting as much as 30% of adults globally. In the United States, this condition incurs an economic burden of over $600 billion annually in healthcare expenses, disability payments, and lost productivity (Huh et al., 2017).

Chronic pain is characterized by persistent or recurrent pain that lasts for at least three to six months, extending beyond the normal healing time of an injury or illness (Milligan & Watkins, 2009). It can be classified into different categories based on its underlying etiology, such as nociceptive, neuropathic, inflammatory, or functional pain. Nociceptive pain results from the activation of specialized pain-sensing nerve fibers in response to tissue damage or inflammation. Neuropathic pain, on the other hand, arises from abnormal neural processing due to damage or dysfunction of the nervous system. Inflammatory pain is associated with immune responses and tissue inflammation. Functional pain refers to pain without identifiable tissue damage or inflammation and is often linked to conditions like irritable bowel syndrome or fibromyalgia (Clauw et al., 2019).

Pain transmission involves a complex interplay of neural circuits and signaling molecules. Nociceptive signals are generated by specialized nerve endings called nociceptors, which respond to noxious stimuli such as heat, pressure, or chemical irritants. These signals are then relayed through the spinal cord to higher brain centers, including the thalamus and somatosensory cortex (Basbaum et al., 2009). The spinothalamic tract is crucial for transmitting pain information from the periphery to the brain. Within the central nervous system (CNS), glial cells are strategically positioned to modulate pain signals, contributing to the processing and modulation of pain perception (Basbaum et al., 2009).

While the exact mechanisms underlying chronic pain are not fully understood, research in recent years has highlighted the significant role of glial cells in the development and maintenance of this condition (Ji et al., 2013). Emerging evidence suggests that glial cells actively participate in the modulation of pain processing. For instance, microglia, when activated, release cytokines such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), which contribute to the sensitization of neurons and the enhancement of pain signals. Astrocytes, in turn, release gliotransmitters like glutamate and ATP, modulating synaptic transmission and contributing to synaptic plasticity. This glial-neuronal interaction potentiates pain pathways and can lead to the maintenance of chronic pain (Guo et al., 2007).

Glial cells, once considered merely supportive cells of the nervous system, are now recognized as key players in chronic pain pathways. This chapter will explore the dysfunctional involvement of glial cells in chronic pain, highlighting peripheral and central nervous system cells.

Neurobiological Basis of Pain Transmission

Under normal circumstances, pain functions as a protective and adaptive sensory system. It acts as a warning signal for the body, indicating tissue inflammation and damage, while also prompting behavioral changes that aid in wound healing and recovery (Basbaum et al., 2009).

In the peripheral nervous system, acute tissue insults like heat, cold, chemical, or mechanical injuries disturb the body's balance and stimulate pain receptors called nociceptors. A variety of inflammatory mediators, derived from damaged tissue or activated mast cells and neutrophils, are released locally in response to injury (Basbaum et al., 2009). These mediators include adenosine 5-triphosphate (ATP),