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Immune Network, the Dangerous Liaisons in Pain: A Short Review

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Abstract

Introduction: Pain has increasingly become an important health problem. However, few doctors at primary health care are qualified to treat it. Recent researches also suggest that neurons are not the only ones involved in the establishment and maintenance of pain. This short review was conceived to collect some information on the contribution of immune system to the pathogenesis of pain and also to shed light to other mechanisms connected to this process.

Development: Inflammation at the damaged site generates a cascade of events that produce innate immune cells concentration and activation; as well as production of pro-inflammatory cytokines, hormonal factors and neurotrophic activators of glial cells, which in turn perturb synaptic transmission. This entire complex induces pain persistence.

Concluding remarks: The recognized commitment of immune, endocrine and nervous cells in pathological changes related with pain is crucial to offer new and satisfactory approaches to solve this problem. Integral modulation of these agents would contribute to new effective alternatives in the handling of pain.

Keywords: Inflammation; Immune System; Pain

Introduction

Pain is a very important and increased health problem [1]. All diseases having pain as a cardinal symptom affect global health, by interfering functional capacity and the sense of well-being of each individual [2].

Almost the 30% of adult's worldwide population report chronic pain as a frequent suffering [3] Pain constitutes one of the habitual reasons of consultation in the contemporary clinical environment. In spite of this, only 15% of the primary health care doctors are qualified to treat it [4].

Recently it has been clarified that neurons are not the only ones involved in the establishment and maintenance of clinical states of pain [4,5]. The nervous system, the endocrine and the immunologic one respond in a coordinated way in the presence of lesions generating pain. This interactive net of lymphoid organs, cells and humoral immunologic elements work interconnected between them and with the other systems trying to protect the organism and to guarantee homeostasis [2]

Even when preclinical data suggest an immune pathogenesis of neuropathic pain, clinical evidence of a central role of the immune system is less clear. This response involves the innate immune system, but evidence also exists of T-lymphocyte recruitment [6].

This article was conceived to collect some information on the contribution of immune system to the pathogenesis of pain and also to shed light to other mechanisms connected to this process.

Development

Pain is one of the cardinal symptoms accompanying inflammation [3]. Inflammatory answer occurs with a main defensive purpose of isolating and destroying the harmful agent, as well as to repair tissues or damaged organs. When it persists chronic inflammation leads to local destruction of the tissues [7].

Chronic pain persistence as a capital problem in medicine has induced multiple clinical investigations that face several difficulties. In the molecular context, many of the experimental discoveries are obtained from animal models. Projections in humans continue being a challenge due to unquestionable ethical restrictions and to the complex control of such variables interfered by subjectivity [1,8].

The clinical and therapeutic current focus in pain essentially confirmed the traditional exclusive neural pattern failure. The interdisciplinary focus emerges as a necessity [1]. Evidences on the interaction of three systems: nervous, endocrine and immunologic one, have been outlined. Those facts are sustained by anatomical and physiological understandings mainly at the molecular level [2,5].

Lymphoid organs have autonomous innervations. When the sympathetic nervous system excitement occurs, the terminal axons release neurotransmitters. The immune system generates cytokines as a response, fundamentally interleukin-1β (IL-1β). This establishes a positive feedback circuit in which participate nervous cells as microglias and astrocytes [5,9].

Furthermore, neural structures stimulate the beginning of a hormonal answer, contributing to the feedback regulation mechanisms. Circulating hormones also assume a neurotransmitter role in the nervous system; all together with the cotransmitter neuropeptide Y. These substances are the catecholamines epinephrine

and norepinephrine, and hormones such as adrenocorticotropic, β-lipotrophin, melanocyte stimulating, corticotropin-releasing (CRH), and β-endorphin [2,10].

The immune and endocrine systems share many spaces in common, too. This interface is evidenced by several hormonal receptors located at immune cell structures [11]. There are CRH raised concentrations at inflamed sites. This outlying production is due to the same immune or nervous cells at the lesion place. CRH induces pro-inflammatory and angiogenic molecules [2,12-13].

Communication among the three systems in the context of pain is recently ratified. The immune system detects the presence of tissue lesion through immunologic messengers. Those are originated in the own lesion site because of sympathetic activation induced by nociceptors; and finally, through the endocrine signaling of the sympathetic-adrenomedullary and hypothalamo-pituitary-adrenocortical axes [14].

Inflammation present in the damaged place generates a cascade of events with innate immune cells concentration and activation; as well as the discharge of immunoactive substances and neurotrophic factors. All this recreates a neuroinflammatory environment that activates glial cells and modulates synaptic transmissions [12,15].

Activated glias also produce pro-inflammatory cytokines IL-1, IL-6 and TNF (tumor necrosis factor) [4,12]. Chemokines such as CC-chemokine ligand 2 (CCL2; also known as MCP1), CXC-chemokine ligand 1 (CXCL1; also known as a keratinocyte-derived chemokine) and CCL7 are produced in astrocytes.3 Those molecules contribute to recruit other near glial cells and to propagate neuroinflammation. Initial glial answers are beneficial but if the stimulation is too intense or continuous it favors pain perpetuation [4,12].

Glial activation is a necessary condition, but not a sufficient one to pain expression. Consequently, microglia could be responsible for the beginning of pain disorders, and astrocytes could be involved in their maintenance [3, 4,15].

Also mast cells are involved in the maintenance of pain and its chronic evolution due to its cytoplasm granules content [16]. Even more, they are considered as main coordinators of immune, nervous and endocrine systems. Because they receive hormonal signals and as well stimulate glias and other immune cells [5,8,17-19]. In human chronic pain, unequivocal demonstration that glial and mast cell activation occurs in hypersensitized patients remains to be provided. Systematic studies are lacking in demonstrating a correlation between the magnitude of glial and/or mast cell markers in the cerebrospinal fluid or in spinal tissue and the intensity of pain in patients [19].

Additionally, the expression of Toll like receptors (TLR) TLR-3, TLR-4, TLR-73, 20 and TLR-920, in neural and endothelial cells located in the dorsal roots ganglion, is recently confirmed. They can be activated by exogenous ligands (known as pathogen-activated molecular patterns, which include viral and bacterial components) and endogenous ligands (known as danger-activated molecular patterns, such as RNAs) [3]. This could be an explicative approach to the way direct nociceptor activation by pathogens occurs [20, 21].

Other soluble and cellular surface molecules are also contributing factors. For instance, integrines (annexin 1) expressed on neutrophil are regulated by glucocorticoids; and the MHC (main histocompatibility complex) antigen class II become overexpressed [13,22].

Macrophages and lymphocyte T helper subpopulations (CD4+) are triggered [23]. The sustained production of inflammatory cytokines profiles goes in detriment of regulatory ones, characterized by IL-10 and transforming growth factor-β (TGF-β). These events achieve continual stages of pain [22].

Concluding Remarks

The recognized commitment of immune, endocrine and nervous cells in pathological changes related with pain is crucial to offer new and satisfactory approaches to solve this problem. This integrative awareness may allow identifying molecular and cellular targets on this complex pathological net to modulate their actions. New researches designing are still a challenge on this area. There are many reasons to discern on immunity related with pain and even more on its dangerous liaisons.

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