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Overview of neurodevelopment and pain research, possible treatment targets

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A B S T R A C T

Pain is a common presenting and often persistent symptom for children with rheumatological disease. Pain is not clearly related to disease severity in children with inflammatory juvenile idiopathic arthritis, and presentations of non-inflammatory musculoskeletal pain are common but there is limited evidence to guide management. Pain assessment must extend beyond measures of pain severity to more fully evaluate characteristics of pain, functional impact and psychosocial effects and family interactions. Evaluation of mechanisms of joint pain in adults has identified potential treatment targets, but additional studies are required as the acute and long-term impacts of pain and injury change during postnatal development. Genotyping, sensory evaluation and neuroimaging may better characterize chronic musculoskeletal pain, identify high-risk groups and/or provide additional outcome measures to monitor disease and treatment progress. An integrated approach to management is required to effectively select and target interventions, reduce pain and disability and improve long-term outcome.

Introduction

Significant neurodevelopmental changes in nociceptive processing occur from infancy through to adolescence that impact on the nature and degree of response to pain and can also influence the

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pharmacodynamic profile of analgesic agents. Due to the enhanced plasticity of the developing nervous system, there is potential for pain and injury in early-life pain to produce long-term changes in sensitivity that are not seen following the same insult at older ages [1–3]. As a result, the ability to extrapolate data obtained from studies in adults may be limited, and the presentation and pathophysiology of diseases associated with chronic pain in paediatric populations differ from those seen in adults. There is a need to increase the quality and quantity of evidence to inform paediatric pain management. Outcome measures that extend beyond isolated measures of pain intensity to more fully characterize pain and its impact are required, with detailed assessment incorporating age- and disease-appropriate measures of activity, sleep and mood and sensory function. An integrated and interdisciplinary approach to management of chronic musculoskeletal pain in children is required to effectively select and target interventions, reduce pain and disability and improve long-term outcomes [4–7]. In this review, data from studies in children and adolescents with inflammatory (e.g., juvenile inflammatory arthritis JIA) or non-inflammatory conditions will be used to illustrate the need for more comprehensive understanding of chronic musculoskeletal pain.

Pain mechanisms

A mechanism-based approach to pain diagnosis and management has been advocated for many years [8,9] and is also relevant to rheumatological conditions [10]. Laboratory models of inflammatory arthritis and osteoarthritis (OA) have been essential for investigating underlying mechanisms and for identifying and assessing potential analgesic targets [11–13]. However, it is clear from studies in young animals that acute and long-term responses to noxious stimuli, peripheral inflammation and nerve or visceral injury change throughout postnatal development [1,2]. Further evaluation of specific age-dependent effects in developmental models of musculoskeletal pain and joint inflammation is warranted [3].

Peripheral nociceptive pathways and sensitization

Peripheral nociceptive pathways sense and transduce noxious stimuli into electrical signals that are transmitted to the central nervous system and synapse in the spinal dorsal horn (see Table 1 for definitions and taxonomy). The joint capsule, ligaments, synovium, periosteum and subchondral bone are densely innervated with peripheral nociceptors. Nociceptors respond to noxious mechanical, thermal or chemical stimuli via a range of receptors, and depolarization results in action potential generation and propagation in peripheral myelinated Aδ fibres and unmyelinated C fibres. In addition, release of neuropeptides (substance P and calcitonin gene-related peptide, CGRP) from peripheral afferent nerves contributes to the inflammatory response (neurogenic inflammation) [14]. In the presence of tissue injury and inflammation, nociceptors in muscle and joint become sensitized, particularly to mechanical stimuli [14]. This state of peripheral sensitization has been specifically identified in electrophysiology recordings of afferent nerves from inflamed joints [13] and is characterized by a reduction in the threshold for activation, an enhanced response to suprathreshold stimuli, and recruitment of previously 'silent' nociceptors [14]. Mediators released from tissue injury and/or the inflamed synovium contribute to sensitization, including pro-inflammatory chemokines and cytokines (e.g., tumour necrosis factor-alpha, TNF-α; interleukin-1, IL-1; IL-6; IL-17), prostaglandins (e.g., PGE_2), neuropeptides (e.g., vasoactive intestinal peptide (VIP) from inflamed synovium) and growth factors (e.g., nerve growth factor (NGF) from articular cartilage, meniscus and synovium) [10,13–16]. Enhanced sensitivity can occur within minutes via phosphorylation and changes in gating properties of ion channels, or over more prolonged periods (e.g., changes in expression of receptors and ion channels) [14].

Receptors involved in peripheral nociception and sensitization following joint inflammation/injury include, but are not limited to, the following:

i) transient receptor protein (TRP) channels comprise a family of non-selective cation channels that transduce thermal and chemical stimuli. The $TRPV_1$ receptor is expressed by nociceptive