

## REVIEWS

## THE DEVELOPMENT OF NOCICEPTIVE CIRCUITS

Marian Fitzpatrick

**Abstract** | The study of pain development has come into its own. Reaping the rewards of years of developmental and molecular biology, it has now become possible to translate fundamental knowledge of signalling pathways and synaptic physiology into a better understanding of infant pain. Research has cast new light on the physiological and pharmacological processes that shape the newborn pain response, which will help us to understand early pain behaviour and to design better treatments. Furthermore, it has shown how developing pain circuitry depends on non-noxious sensory activity in the healthy newborn, and how early injury can permanently alter pain processing.

**Keywords:** nociception; newborn; CNS; Neurotrophic factors — nerve growth factor (NGF), neurotrophin-4 (NT-4), brain-derived neurotrophic factor (BDNF) — are thought to be of major importance in the response. This is possible because the NGF, BDNF and NT-4 are secreted by the injured tissue.

After years of neglect, the study of infant pain has emerged as one of the most interesting and important areas of pain research today. It provides a fascinating insight into how sensation neurons connect together to analyse and process nociceptive events, and illustrates how the growing nervous system deals with events that threaten its structural integrity and survival. It also has the potential to provide us with a neurobiological basis for pain assessment and treatment in human infants.

Newborn infants show strong pain behaviour, but the study of the development of nociceptive pathways shows that these pain sensitive, functional signalling pathways that are not found in the mature nervous system, in healthy individuals. Recent research into the development of inhibitory and excitatory synaptic transmission has provided new insights into the crucial changes that shape pain pathways in the first postnatal weeks.

This review focuses on the underlying organization and maturation of nociceptive circuitry in the dorsal horn during the first postnatal weeks and on recent data that show how that circuitry might be altered by sensory inputs in early life. It begins with the specification of nociceptive neurons — recent studies have identified key molecular pathways that control the genesis of spinal nociceptive circuits. It then traces the formation of functional synapses, neural circuits and

nociceptive reflexes, emphasizing recent research on the postnatal developmental regulation of excitatory and inhibitory synaptic transmission in the developing dorsal horn. Finally, the role of sensory activity — from both non-noxious and nociceptive stimulus inputs — in influencing the development of pain processing is reviewed and the implications for human infant pain discussed. Ultimately, we argue that we need to use this research to design better strategies for the relief of pain in infants and children.

#### Early specification of nociceptive neurons

Nociceptive neurons are specified early in development, long before they form contacts with their distant peripheral or central targets. Sensory subtypes are determined even before neural crest cells become committed to neuronal or glial fates<sup>1</sup>. Different classes of sensory neurons in dorsal root ganglia (DRG) are generated in two waves: large diameter neurons (small nociceptor C- and B-expressing [TRAC<sup>+</sup> and TRB<sup>+</sup>] neurons) are born first, followed by small diameter TRKA<sup>+</sup> neurons<sup>2,3</sup>. Recently, an even later wave of nociceptive neurons has been shown to arise from boundary cap cells, which are neural crest derivatives that migrate down the root from the dorsal root entry zone<sup>4</sup>. All these neurons require neurogenin 1 or 2 (NG2/NG2) — two neuronal differentiation genes that encode basic helix-loop-helix (bHLH) transcription factors

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# Regulation Of Hemodynamic Nociceptive Reactions Vol 2 Pt 12 Neuropharmacology Reviews

**Xiang Xie**



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