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Review

Therapeutic opportunities for pain medicines via targeting of specific translation signaling mechanisms

Salim Megat, Theodore J. Price*

School of Behavioral and Brain Sciences, The University of Texas at Dallas, USA

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ABSTRACT

As the population of the world ages and as more and more people survive diseases that used to be primary causes of mortality, the incidence of severe chronic pain in most of the world has risen dramatically. This type of pain is very difficult to treat and the opioid overdose epidemic that has become a leading cause of death in the United States and other parts of the world highlights the urgent need to develop new pain therapeutics. A common underlying cause of severe chronic pain is a phenotypic change in pain-sensing neurons in the peripheral nervous system called nociceptors. These neurons play a vital role in detecting potentially injurious stimuli, but when these neurons start to detect very low levels of inflammatory meditators or become spontaneously active, they send spurious pain signals to the brain that are significant drivers of chronic pain. An important question is what drives this phenotypic shift in nociceptors from quiescence under most conditions to sensitization to a broad variety of stimuli and spontaneous activity. The goal of this review is to discuss the critical role that specific translation regulation signaling pathways play in controlling gene expression changes that drive nociceptor sensitization and may underlie the development of spontaneous activity. The focus will be on advances in technologies that allow for identification of such targets and on developments in pharmacology around translation regulation signaling that may yield new pain therapeutics. A key advantage of pharmacological manipulation of these signaling events is that they may reverse phenotypic shifts in nociceptors that drive chronic pain thereby creating the first generation of disease modifying drugs for chronic pain.

Phenotypic changes in nociceptors drive chronic pain and require changes in gene expression

A key feature of many chronic pain states is a persistent change in the sensitivity of nociceptors that outlives the tissue healing process (Price and Inyang, 2015; Price and Gold, 2017). This results in hypersensitivity to mechanical stimulation, thermal hyperalgesia and, in many cases, spontaneous pain (Campbell and Meyer, 2006). Clinical studies consistently demonstrate that blocking peripheral input from sensitized nociceptors rapidly attenuates pain in chronic pain patients (Haroutounian et al., 2014; Vaso et al., 2014). These findings provide compelling evidence for the hypothesis that chronic pain requires a peripheral driver and that peripheral driver is likely to be sensitized or spontaneously active nociceptors. Preclinical studies also provide compelling evidence for this hypothesis. For instance, after a nerve injury that causes neuropathic pain, axons that sprout back into the injured area are sensitized to mechanical stimulation and this sensitization persists even after these nerve endings re-innervate their target organ (Jankowski et al., 2009). Very recent evidence suggests that mechanically gated channels in A-type nociceptors change their gating properties after injury providing a possible biophysical basis for some forms of mechanical hypersensitivity after injury (Weyer et al., 2015). Mechanisms governing thermal hyperalgesia are now very well understood and involve alterations in the function of TRPV1 (for heat) and TRPM8 (for cold). Finally, the biophysical basis of injury-induced emergence of spontaneous activity in nociceptors is starting to be elucidated (Price and Gold, 2017). This involves changes in expression (Tsantoulas et al., 2012; Laumet et al., 2015; Calvo et al., 2016) and function of voltage-gated channels (Gold et al., 2003) that leads to subthreshold membrane oscillations which subvert the stability of the resting membrane potential making these neurons susceptible to ectopic action potential generation (Devor, 2006).

Key questions emerging from these findings are: how do these injury-induced changes in nociceptor function occur and why do they so frequently persist after an injury has healed. The central theses of this review are: 1) that these changes in nociceptor function require changes in gene expression, 2) that these changes in gene expression can be persistent once they are turned on, 3) that these changes in gene

* Corresponding author at: UTD, BSB14.102, 800 W Campbell Rd, Richardson, TX 75080, USA.
E-mail address: Theodore.price@utdallas.edu (T.J. Price).

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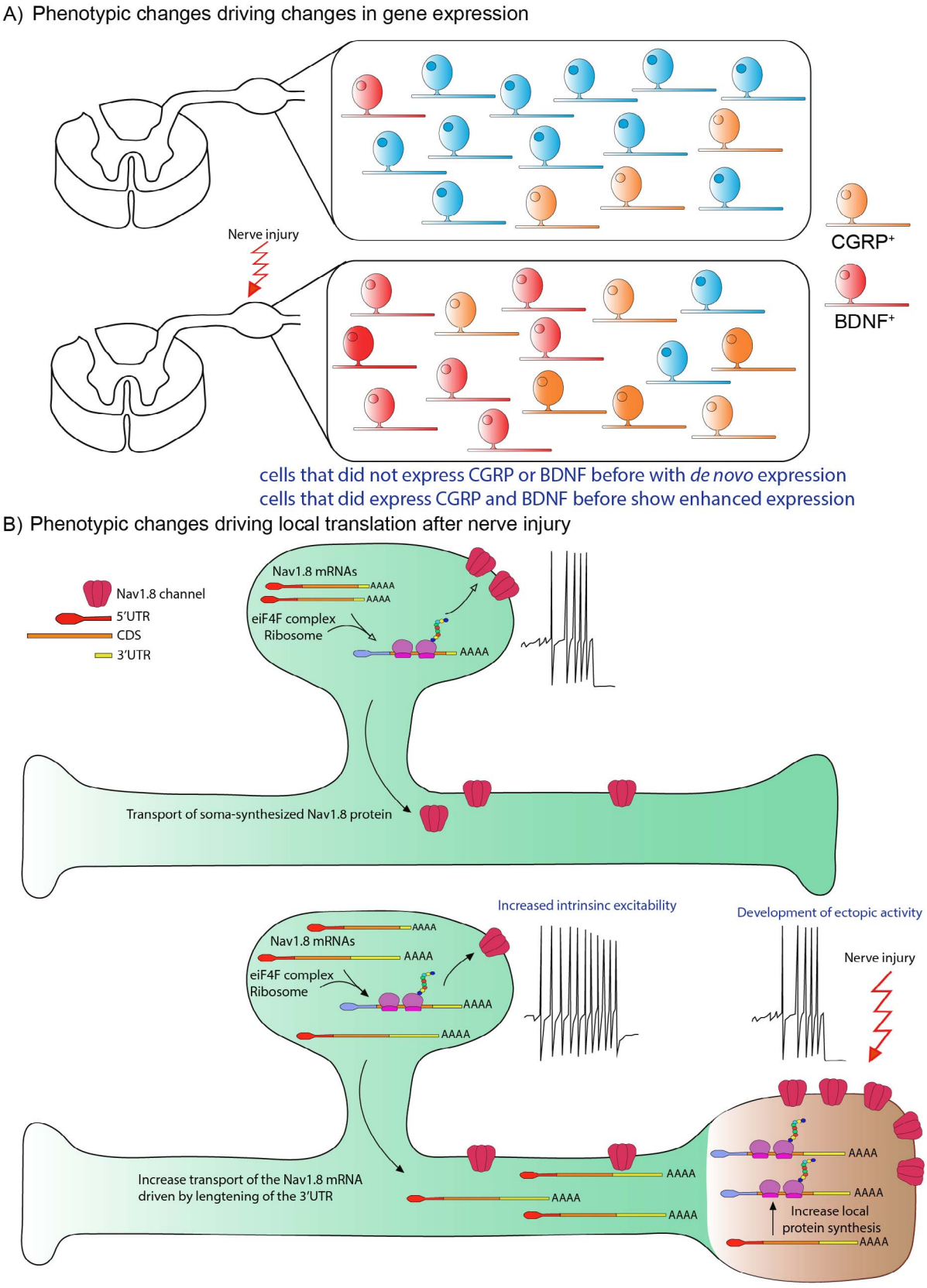

Fig. 1. Phenotypic changes in DRG neurons associated with nerve injury and neuropathic pain A) Nerve injury can produce phenotypic changes leading to changes in expression for a variety of different peptides or proteins, including BDNF or CGRP. These include changes in expression in cells that already expressed these genes (brighter colors) or *de novo* expression in cells that did not previously express these genes. B) A second sort of phenotypic change involves altered translational control. For instance, after nerve injury Nav1.8 mRNA is increasingly trafficked into the axon and is locally translated at sites of injury contributing to altered excitability and potentially ectopic discharges.