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Translation regulation in the spinal dorsal horn – A key mechanism for development of chronic pain

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ABSTRACT

Chronic pain is a pathological condition characterized by long-lasting pain after damaged tissue has healed. Chronic pain can be caused and maintained by changes in various components of the pain pathway, including sensory neurons, spinal cord and higher brain centers. Exaggerated sensitivity and responsiveness of spinal nociceptive circuits, representing maladaptive plasticity, play key roles in the amplification of peripheral signals in chronic pain conditions. This spinal amplification mechanism profoundly contributes to the development and maintenance of chronic pain hypersensitivity in response to peripheral injury, and in some cases occurs independently of the peripheral stimulus. Long-lasting changes in the activity of spinal neurons are caused by alterations in their cellular proteome, which relies on *de novo* gene expression. Recent evidence indicates that translational control of gene expression plays a major role in determining protein levels, and is intricately involved in different forms of intrinsic and synaptic plasticity. In this review, we summarize findings supporting a key role for translational control in spinal cord-dependent mechanisms of chronic pain, and present recent approaches to reverse persistent pain by targeting these mechanisms.

Introduction

Peripheral injury causes acute pain, which is essential for an organism's survival by ensuring quick withdrawal from harmful or potentially harmful stimuli. Under most circumstances, pain resolves shortly after damaged tissue heals. However, in some cases, the pain does not subside and persists after full tissue recovery. This type of pain, called chronic pain, does not serve any protective function and is likely driven by pathological changes that can arise in different components of the pain pathway. Long-lasting sensitization of primary sensory neurons and spinal nociceptive circuits, and plastic changes in brain regions, have all been associated with enhanced transmission and sensation of pain. In this review, we will focus on the spinal cord dorsal horn, which integrates inputs from peripheral and descending pathways to generate an output that is transmitted up to the brain. First, we will briefly describe the mechanisms underlying the sensitization of spinal pain circuits, and then present evidence for the role of translational control in the regulation of these processes.

Mechanisms underlying sensitization of spinal nociceptive circuits

In chronic pain conditions, repeated or intense noxious stimuli lead to maladaptive plastic changes along the pain pathway, including a sensitization of spinal nociceptive circuits, a phenomenon known as central sensitization (Woolf, 2011). Central sensitization is considered to be a key mechanism underlying the development of persistent hypersensitivity states (Latremoliere and Woolf, 2009). Alterations in several cellular processes can contribute to central sensitization, including enhanced postsynaptic response of spinal neurons to neurotransmitter release from primary afferents (Ikeda et al., 2003, 2004), reduced inhibitory tone as a result of decreased excitability of spinal inhibitory interneurons (Guo and Hu, 2014; Torsney and MacDermott, 2006), and inefficient GABAergic and glycinergic neurotransmission (Coull et al., 2003), as well as modulation of descending pathways (Ossipov et al., 2014). An imbalance of excitatory versus inhibitory activity in central sensitization leads to enhanced excitability of spinal nociceptive circuitry, which causes an amplification of the peripheral signal. Central sensitization results in a reduced pain threshold (allodynia), an increase in the perceptual response to noxious stimuli (hyperalgesia), and a recruitment of peripheral inputs from non-injured

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areas, causing an expansion of the receptive field (secondary hyperalgesia).

Translational control of neuronal plasticity

Long-lasting modulation of intrinsic excitability and synaptic functions relies on new gene expression. Gene expression can be modulated at different steps: transcription, mRNA translation, mRNA and protein stability, and post-translational modifications of protein. Translational control allows for the modulation of the cellular proteome by regulating the efficiency by which mRNA is translated into proteins. It provides neurons with a mechanism to quickly and locally respond to intracellular stimuli and extracellular cues by modifying their cellular or synaptic proteome.

Translational control mechanisms

mRNA translation can be divided into three stages: initiation, elongation and termination. Initiation is the rate limiting step for translation and therefore is tightly regulated by several mechanisms (Sonenberg and Hinnebusch, 2009). At their 5′ end, all nuclear transcribed eukaryotic mRNAs contain a structure called 7 methylguanosine triphosphate (m^7Gppp), termed the “cap”. This structure facilitates ribosome recruitment to the mRNA (Fig. 1). The 3′ end of the mRNA contains a poly(A) tail that protects mRNA from degradation, and binds poly(A)-binding protein (PABP). The mechanisms regulating translation initiation can be divided into two major categories: (1) regulation of the recruitment of the ribosome to the cap at the 5′ end of mRNA (via phosphorylation of translation initiation factors such as 4E-BPs, eIF4E and eIF2a), and (2) regulation of translation at the 3′ end of mRNA via controlling the length of the poly(A) tail (e.g. by CPEB).

Ribosome recruitment requires a group of translation initiation factors, termed eIF4 (eukaryotic initiation factor 4). A critical member of this group is eIF4F, which is a three-subunit complex (Edery et al., 1983; Grifo et al., 1983) composed of (1) eIF4A (an RNA helicase), (2) eIF4E, which specifically interacts with the cap structure (Sonenberg et al., 1979) and (3) eIF4G, a large scaffolding protein that binds to both eIF4E and eIF4A. eIF4G serves as a modular scaffold that assembles the protein machinery to direct the ribosome to the mRNA (Fig. 1). eIF4E generally exhibits the lowest level of expression of all eukaryotic initiation factors. It plays a central role in cap-recognition, and due to its low levels of expression, it is considered the rate-limiting step for translation, and a major target for regulation. The assembly of eIF4F is promoted by the mechanistic target of rapamycin complex 1 (mTORC1), which phosphorylates and thereby inactivates translational repressors, the eIF4E-binding proteins (4E-BP1, 4E-BP2 and 4E-BP3). 4E-BPs repress the formation of the eIF4F complex by competing with eIF4G for a common binding site on eIF4E. Upon phosphorylation by mTORC1, 4E-BP binding to eIF4E is reduced, allowing eIF4F complex formation and initiation of translation. mTORC1 also phosphorylates its second major downstream effectors, p70 S6 kinases (S6K1/2), which regulate translation initiation (via eIF4B), translation elongation (via eEF2K) and ribosome biogenesis (via ribosomal protein S6).

eIF4E activity is also regulated via phosphorylation at serine 209 by MNK1/2 (mitogen-activated protein kinase (MAPK) interacting protein kinases 1/2) downstream of ERK (extracellular-signal-regulated kinase) (Fig. 1). This phosphorylation event is associated with increased rates of translation initiation (Gkogkas et al., 2014; Scheper et al., 2002), although the exact underlying molecular mechanism remains unknown.

A second major translational control mechanism is mediated by the translation initiation factor, eIF2 (composed of three subunits) (Sonenberg and Hinnebusch, 2009), via phosphorylation of its α subunit (Fig. 1). Translation initiation requires the formation of a ternary complex composed of the initiator (Met-$tRNA_i^{Met}$) and the GTP-bound eIF2. At the end of each round of ribosome recruitment, there is a recycling of inactive GDP-bound eIF2α to active GTP-bound eIF2 by the guanine nucleotide exchange factor (GEF), eIF2B (Pavitt et al., 1998). Phosphorylation of eIF2α at serine 51 inhibits the activity of eIF2B, reducing ternary complex formation and thereby inhibiting protein synthesis. Paradoxically, eIF2α phosphorylation stimulates translation of mRNAs containing upstream open reading frames (uORFs) in their 5′ UTRs, such as ATF4 and CHOP. eIF2α is phosphorylated in response to different cellular stress conditions via activation of eIF2α kinases (PERK, PKR, GCN2 and HRI) (Trinh and Klann, 2013). Phosphorylation of eIF2α is largely involved in the regulation of general translation, whereas eIF4E-dependent translational control regulates the translation of a distinct subset of mRNAs, many of which are involved in proliferation, growth and synaptic plasticity.

Translation is also regulated via 3′ end-mediated mechanisms. Translation of mRNAs containing the cytoplasmic polyadenylation elements (CPE) at their 3′ UTR is regulated by the cytoplasmic polyadenylation element-binding protein (CPEB) (Richter and Klann, 2009). CPEB binds CPE and stimulates the prolongation of the poly(A) tail by regulating the polyadenylation apparatus composed of poly(A) polymerase Gld2, deadenylase PARN, and translational factor neuroguidin (Ngd) (Ivshina et al., 2014; Udagawa et al., 2012). Elongation of the mRNA poly(A) tail leads to stabilization of the mRNA and enhanced binding of the poly(A)-binding protein (PABP), which facilitates translation initiation by simultaneously binding to both the poly(A) tail and eIF4G, resulting in mRNA circularization (Gray et al., 2000; Kahvejian et al., 2001). This mechanism has been shown to regulate the translation of *CamkIIα* and *Nr2a* mRNAs (Huang et al., 2002; Wu et al., 1998).

Synaptic plasticity

Synaptic plasticity refers to the ability of the synapse to strengthen or weaken in response to experience or stimuli. The predominant cellular model for synaptic plasticity is long-term potentiation (LTP), which is thought to underlie learning and memory (Morris, 2003). Co-activation of pre- and post-synaptic compartments triggers calcium influx into neurons, stimulating several signaling pathways to promote transcription and translation of plasticity-related genes. The newly synthesized mRNAs are either subsequently translated in the cell body or transported to synapses where they are locally translated (Jung et al., 2014; Tom Dieck et al., 2014). The local protein synthesis model is consistent with the presence of translation machinery (ribosomes and translation factors) and mRNAs in, or close to dendritic spines (Steward and Fass, 1983; Steward and Levy, 1982). Moreover, LTP-inducing stimulation causes ribosomes to move from dendritic shafts to spines with enlarged synapses (Ostroff et al., 2002). Protein synthesis in dendrites occurs in response to various forms of stimulation (Kang and Schuman, 1996; Scheetz et al., 2000) and is essential for long-term plasticity (Huber et al., 2000; Kang and Schuman, 1996). Accordingly, studies in the hippocampus, amygdala and cortex have demonstrated a key role of translational control in the protein synthesis-dependent late phase of long-term potentiation (L-LTP), long-term depression (LTD) and learning and memory (Costa-Mattioli et al., 2009). Inhibition of translation with anisomycin or inhibitors of mTORC1 impairs L-LTP and long-term memory (LTM) (Cammalleri et al., 2003; Tang et al., 2002). Neuronal activity and behavioural training lead to a reduction in eIF2α phosphorylation, resulting in suppression of LTD and stimulation of L-LTP and long-term memory (Costa-Mattioli et al., 2005; Costa-Mattioli et al., 2007; Costa-Mattioli and Sonenberg, 2006; Di Prisco et al., 2014). Regulation of translation via CPEB and PABP has been also shown to control L-LTP and LTM (Alarcon et al., 2004; Khoutorsky et al., 2013; Richter, 2007; Udagawa et al., 2012).

Most of the current knowledge on the role of translational control in neuroplasticity has been derived from experiments in the hippocampus, however recent studies show that similar mechanisms regulate activity-dependent long-term modification of synaptic strength in other brain areas including cortex, amygdala, and spinal cord (Belelovsky et al.,