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**Role of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor regulation in stress-induced pain chronification**

Liu S *et al*. AMPA in stress-induced pain chronification

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**Abstract**

Persistent postsurgical pain is a serious issue in public health, which has received increased interest in recent years. Previous studies have reported that psychological factors promote the development of chronic postsurgical pain. However, it is unclear how chronification of postsurgical pain occurs. The α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA) phosphorylation in the central nervous system plays a critical role in synaptic plasticity and contributes to central sensitization and chronic pain development. Here, we discuss the role of AMPA receptor regulation in stress-induced pain chronification after surgery.

**Key words:** Pain chronification; Stress; α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor phosphorylation

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**Core tip:** Theα-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor phosphorylation contributes to stress-induced pain chronification after surgery.

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**PAIN CHRONIFICATION AFTER SURGERY**

After surgery, patients experience either short-term or long-lasting pain. In some patients, pain post-surgery can persist even after surgical incision has recovered. Chronic postsurgical pain is primarily neuropathic in nature. As we know, acute postoperative pain is an adaptive response to surgical damage, but chronic postsurgical pain is maladaptive since it is not protective. However, the central mechanisms underlying pain chronification after surgery remain to be illustrated[1].

Pain chronification after surgery is a process involving multiple biological systems[2]. Chronic postsurgical pain provides a special opportunity to understand pathogenic mechanisms for the transition from acute to chronic pain. Previous studies have indicated that psychological factors promote the development of chronic postsurgical pain[3,4]. Psychological stress can disturb the physiological homeostasis of an organism[5,6]. People who experience stress in their early life or even before birth may have chronic susceptibility to developing pain in their whole life[7]. Thus, it is very possible that early stress could cause permanent changes in pain signaling in the central nervous system. In addition, surgery produces the release of inflammatory mediators, such as prostaglandins and cytokines[8], which can sensitize primary sensory afferents. Stress might increase sensitivity to the hyperalgesic effects of proinflammatory cytokines[9]. Moreover, stress-induced hyperalgesic priming, a neuroplastic change in primary afferent nociceptors, has been implicated in chronic generalized pain syndromes and other chronic pain conditions[10-15]. Therefore, stress may be involved in the development of chronic pain after surgery.

**STRESS ENHANCES AMPA RECEPTOR REGULATION AND SYNAPTIC PLASTICITY**

Psychological stress produces physiological and behavioral changes that cause long-term adaptive responses[5]. Two major reactions can occur in response to stress. One reaction after stress is rapid activation of the autonomic nervous system and subsequent release of the stress hormones epinephrine and norepinephrine[16]. Norepinephrine can activate cAMP-dependent protein kinase and calcium/calmodulin-dependent protein kinase II[17,18], which can phosphorylate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluA1 at the Ser845 and Ser831 sites, respectively[19-21]. Targeted mutant mice with the mutations of these phosphorylation sites that block phosphorylation at Ser845 and Ser831 sites of GluA1 display impairment in synaptic plasticity and learning[22]. Thus, stress through releasing the stress hormone norepinephrine can induce GluA1 phosphorylation at the Ser831 and Ser845 sites and then facilitate long-term potentiation induction[23]. Phosphorylation at these sites is sufficient to reduce the threshold for GluA1 synaptic incorporation during long-term potentiation[23]. Another reaction after stress is the stimulation of the hypothalamus–pituitary–adrenal axis and subsequent release of the stress hormone glucocorticoids (a type of corticosteroid hormone) from the adrenal glands[16]. Glucocorticoids are able to bind to two types of receptors in the central nervous system: [mineralocorticoid receptor](http://www.nature.com.ezproxy.welch.jhmi.edu/nrn/journal/v11/n10/glossary/nrn2913.html#df5)s and glucocorticoid receptors. [Mineralocorticoid receptor](http://www.nature.com.ezproxy.welch.jhmi.edu/nrn/journal/v11/n10/glossary/nrn2913.html#df5)s have a high affinity for corticosterone (the main glucocorticoid in rodents) and are bound when the hormone level is low. Glucocorticoid receptors have a lower affinity for corticosterone than do [mineralocorticoid receptor](http://www.nature.com.ezproxy.welch.jhmi.edu/nrn/journal/v11/n10/glossary/nrn2913.html#df5)s, which are activated only when the hormone level is high enough[16]. Both [mineralocorticoid receptor](http://www.nature.com.ezproxy.welch.jhmi.edu/nrn/journal/v11/n10/glossary/nrn2913.html#df5)s and glucocorticoid receptors are expressed in the central nervous system[16,24]. By activating the two receptor subtypes, corticosterone rapidly and persistently regulates AMPA receptor GluA2 trafficking, which plays an important role in synaptic transmission and plasticity[5,25]. Therefore, the stress hormone corticosterone can effectively enhance the synaptic content of AMPA receptors and then produce synaptic potentiation[5,25].

**MECHANISMS UNDERLYING STRESS-INDUCED PAIN CHRONIFICATION AFTER SURGERY**

After injury and injury-induced pain, a “supersystem” consisting of nervous system, endocrine system, and immune system may act together to regulate the functional activities in these systems[26]. Thus, the development of chronic postsurgical pain could be caused by dysregulation of the supersystem. For instance, the nervous system and endocrine system can cooperate in the response to stress, which has been referred to as the neuroendocrine stress response[26]. Recently, we have utilized these concepts to develop a new animal model to study acute-to-chronic pain transition after surgery. In this model, we found that social defeat stress enhances plantar incision-induced spinal AMPA receptor phosphorylation and thereby prolongs incisional pain and that stress hormones regulate AMPA receptor activities in the spinal cord during the pain prolongation[27]. We also found that the social defeat stress not only increases GluA1 membrane expression, but also enhances GluA2 intracellular expression in the spinal dorsal horn neurons[27]. Our study identifies stress as a risk factor for pain chronification after surgery. Our recent study indicates that intrathecal injection of a Ca2+-permeable AMPA receptor blocker significantly inhibits the stress-induced postsurgical pain prolongation (unpublished data). Therefore, we hypothesize that by releasing two types of stress hormones (norepinephrine and corticosterone), stress regulates AMPA receptor activities (such as phosphorylation and trafficking), which leads to GluA1 membrane insertion and GluA2 internalization and causes a switch from Ca2+-impermeable (GluA2-containing) to Ca2+-permeable (GluA2-lacking) AMPA receptors. This switch will enhance Ca2+ influx and further activate Ca2+-dependent protein kinases, thereby promoting AMPA receptor phosphorylation and other phosphorylation-triggered activities (Figure 1). This positive feedback loop may contribute to the molecular mechanisms that underlie stress-induced pain chronification after surgery.

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**Figure 1 Mechanisms underlying stress-induced pain chronification after surgery.** Note that α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor switch from Ca2+-impermeable (GluA2-containing) to Ca2+-permeable (GluA2-lacking) will enhance Ca2+ influx and further activate Ca2+-dependent protein kinases, thereby promoting AMPA receptor phosphorylation and other phosphorylation-triggered activities.