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Editorial

Role of Stress in the Transition from Acute To Chronic Pain after Surgery

Sufang Liu[1,2], Changsheng Li[1,2], Ying Xing[2,3] and Feng Tao[1]*

[1]Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[2]Basic Medical College, Zhengzhou University, Zhengzhou, Henan, China

[3]Basic Medical College, Xinxiang Medical University, Xinxiang, Henan, China

***Corresponding author:** Feng Tao, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, 720 Rutland Ave. / Ross 355, Baltimore, MD 21205, Maryland, USA

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Pain is a hallmark of tissue damage and inflammation, which promotes tissue protection and thereby contributes to repair. Thus, transient acute pain is an important feature of the adaptive response to damage. However, pain can persist for months to years after surgery even though the surgical incision that originally caused the pain has recovered. Such chronic neuropathic pain is maladaptive because it no longer serves as a protective reaction. Chronic pain, especially chronic neuropathic pain, is debilitating, both physiologically and psychologically, and treatments to provide relief from chronic pain are often ineffective. To date, the neurobiological mechanisms that underlie the transition from adaptive acute pain to maladaptive chronic pain are not fully understood [1].

The transition from acute to chronic postsurgical pain is a complex and poorly understood developmental process [2]. Chronic postsurgical pain provides a special opportunity to understand pathogenic mechanisms for the transition from an acute to a chronic pain state. Previous studies have indicated that psychosocial and socio-environmental factors are associated with the development of chronic postsurgical pain [3,4]. Stress is generally defined as any conditions that disturb the physiological or psychological homeostasis of an organism [5,6]. Exposure of humans to stress early in life, or even before birth, can induce life-long chronic susceptibility to developing pain syndromes [7]. Thus, it is an intriguing possibility that early stress could trigger permanent changes in pain pathways in the central nervous system. In addition, surgery causes the release of inflammatory mediators, such as prostaglandins and cytokines [8], which activate and sensitize primary sensory afferents. Stress can induce a sustained condition of increased 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 pathogenesis of chronic neuropathic pain after surgery.

Exposure to stressful events induces physiological and behavioral changes that promote long-term, adaptive responses to such disturbances [5]. One of the core reactions in response to a stressful event is the rapid activation of the autonomic nervous system and subsequent release of epinephrine and norepinephrineinto the circulation [16]. Norepinephrine can activate cAMP-dependent protein kinase and calcium/calmodulin-dependent protein kinase II [17,18]. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor GluA1 Ser831 is phosphorylated by calcium/calmodulin-dependent protein kinase IIand protein kinase C, whereas GluA1 Ser845 is phosphorylated by cAMP-dependent protein kinase [19-21]. Genetically modified mice with knockin mutations that block phosphorylation at Ser845 and Ser831 sites of GluA1 show disturbances in synaptic plasticity and learning [22]. Thus, the stress hormone norepinephrine can induce GluA1 phosphorylation at Ser831 and Ser845 sites and thereby facilitate long-term potentiationinduction [23]. Phosphorylation at these sites is necessary and sufficient to lower the threshold for GluA1 synaptic incorporation during long-term potentiation [23]. In addition, stressful events stimulate the hypothalamus–pituitary–adrenal axis, and glucocorticoids, a type of corticosteroid hormone, are released from the adrenal glands after exposure to a stressful event [16]. Glucocorticoids can enter the central nervous system and bind to two subtypes of receptors: mineralocorticoid receptors and glucocorticoid receptors. Mineralocorticoid receptors has a high affinity for glucocorticoids and is therefore occupied when hormone levels are low. Glucocorticoid receptors have a 10-fold lower affinity for corticosterone (the main glucocorticoid in rodents) than do mineralocorticoid receptors and therefore become activated only when hormone levels rise after stress [16]. Both mineralocorticoid receptors and glucocorticoid receptors are localized in the central nervous system [16,24]. Through activation of the two receptor subtypes, corticosterone rapidly and persistently regulates AMPA receptor GluA2 trafficking, which is crucially involved in synaptic transmission and plasticity [5,25]. Thus, the stress hormone corticosterone can effectively condition the synaptic content of AMPA receptors and then trigger synaptic potentiation [5,25].

Neurotransmitters, peptides, hormones, and cytokines in the nervous, endocrine, and immune systems act together as a sort of "supersystem" in response to physical injury and injury-produced pain [26]. Thus, the development of chronic neuropathic pain after surgery may be caused bydysregulation of the supersystem. In the supersystem, the nervous and endocrine systems cooperate in the stress response, which has been referred toas the neuroendocrine

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stress response[26]. Recently, we have utilized these concepts to develop a new animal model to study pain transition. In this model, spinal AMPA receptor activities after surgery and their regulation by stress hormones are combined to induce chronic postsurgical pain. Our study will identify stress as a risk factor forthe development of chronic neuropathic pain after surgery.This novel concept will help us predict which patients are at greater risk for developing chronic pain after surgical procedures. Eventually, monitoring of stress hormone levels in the blood may help physicians improve pain control in high-risk patients.

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