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Stress and Pain

Jamie L. Rhudy, Emily J. Bartley and Shreela Palit
Department of Psychology, The University of Tulsa, Tulsa, OK, USA

Synonyms

Appraisal; Biobehavioral factors; Coping; Physiological pathways; Psychosocial factors

Definition

Homeostasis – The process of maintaining the body’s physiology within an optimal range (e.g., temperature, pH, oxygen level), despite constant demands that attempt to alter physiological levels.

Allostasis – A term that has replaced the idea of homeostasis, in that it recognizes that the body’s optimal range can be achieved by a number of different strategies and that the optimal range may vary depending on the situation.

Stress – A term that refers to a disturbance of the body’s homeostasis. In colloquial terms, it is often used to refer to the negative emotional experiences (e.g., anxiety, fear) that co-occur with disrupted homeostasis.

Stress response – The body’s compensatory reaction to a homeostatic challenge, which attempts to restore equilibrium.

Pain – An unpleasant sensory and emotional experience associated with tissue damage or described in terms of such damage, which serves as an alarm system for internal and external sources of threat.

Nociception – The process by which neural signals associated with noxious stimulation are transmitted throughout the nervous system.

Introduction

For a thorough overview of stress, see Sapolsky (2004) or Lovallo (2005). The concept of physiological stress was first introduced by William Cannon in the 1930s. His work elucidated the role of the sympathetic nervous system and the endocrine system in reaction to threat, and demonstrated that when faced with a threat, resources are mobilized (e.g., increased heart rate, respiration, blood flow to large muscles) to help an organism combat or flee the source of the stress (i.e., fight or flight response). However, the notion of stress was later popularized in the 1950s by Hans Seyle who noted that repeated or prolonged physical stressors (e.g., cold, sleep deprivation, infection) caused an organism to move through three stages, that is, alarm, resistance, and exhaustion, a pattern he called the general adaptation syndrome. He found that, regardless of the type of stressor, the physiological consequences of exhaustion were similar and included enlarged adrenal cortex, decreased...
thymus and lymph glands, and ulceration of the stomach and duodenum. This illustrated that intense, prolonged, or repeated stressors can have detrimental physiological effects. More recently, the term “allostatic load” has been used by McEwen and others to refer to the physiological costs of chronic exposure to stress and the cumulative wear and tear on the multiple systems that regulate allostasis.

Lazarus and Folkman proposed that the stress response is influenced by the cognitive appraisal of the stressor. If a person believes that he/she has the resources available to handle the threat, then the threat will elicit very little stress. However, if the person believes their resources are not adequate to handle the threat, then the threat will elicit considerable stress. It is now known that a number of different variables can impact stress appraisals and the stress response, such as the predictability or controllability of the stressor (Lovallo 2005). Importantantly, when coping resources are inadequate, negative emotions are elicited (e.g., distress, anxiety, fear) that also contribute to the stress response.

The two primary “arms” of the stress response are the hypothalamic-pituitary-adrenocortical (HPA) axis and the hypothalamic-sympathetic-adrenomedullary (HSAM) system. When a stressor activates the HPA axis, this causes the hypothalamus to release corticotropin-releasing hormone (CRH), thus stimulating pituitary to release ACTH, that in turn elicits the release of glucocorticoids from the adrenal cortex. For humans, cortisol is the most important stress-related glucocorticoid. When stress activates the HSAM, this causes the hypothalamus to communicate with the brain stem nucleus of the solitary tract (NST). The NST promotes sympathetic outflow that in turn stimulates the adrenal medulla to release epinephrine (adrenaline) and norepinephrine (noradrenaline). Epinephrine is the more important of the two in the stress response. It is the output of the HSAM that produces responses most associated with fight or flight. The HPA and the HSAM can be activated by sensory channels involved with the detection of external and internal threats (e.g., predator, pain); however, these stress systems are also modulated in a top-down manner from higher brain centers (e.g., prefrontal cortex, limbic system) involved with emotion, evaluation, and planning (Lovallo 2005). Thus, it is through these top-down connections that emotion, appraisals, and coping efforts can moderate the stress response, but also how mental activities, such as rumination, worry, and anticipation, can elicit a stress response in the absence of an immediate threat. While HPA and HSAM represent the two major arms of the stress response, the consequences of stress are wide-ranging, affecting all body systems (e.g., cardiovascular, immune, gastrointestinal, neurological, endocrine, reproductive).

Pain Systems and Connections to the Stress Systems

For a thorough overview of the ascending pain pathway, see other sections in the Encyclopedia of Pain (e.g., Nociception in Superficial Tissue, Musculoskeletal, Articular, and Visceral Nociception, Ascending Nociceptive Pathways, Nociceptive Processing in the Thalamus, Nociceptive Processing in the Limbic System and Cerebra). Briefly, primary afferent (nociceptors) relay the pain signal to the dorsal horn of the spinal cord where the message is then relayed to supraspinal centers by several ascending tracts, including the spinothalamic, spinohypothalamic, spinoreticular, spinoparabrachial, spinocervicothalamic, postsynaptic dorsal column projection, and spinosensory cortices. Once the signal reaches the brain it undergoes parallel processing in a number of brain regions, including the thalamus, brain stem (including the nucleus of the solitary tract), anterior cingulate cortex, insula, amygdala, hypothalamus, and somatosensory cortices. It is this supraspinal processing within this circuitry referred to as the pain neuromatrix that eventually leads to the subjective experience of pain (Melzack 1999). Because of these ascending connections to regions involved with the arms of the stress response (i.e., hypothalamus, nucleus of the solitary tract), pain signaling can directly activate a stress response.

In addition to the ascending pain pathway, there is a descending pain pathway that allows
for the inhibition and facilitation of pain signaling (for a thorough overview, see other sections in the Encyclopedia of Pain, i.e., Descending Modulation of Nociceptive Processing, Descending Circuits in the Forebrain Imaging, Descending Facilitatory Systems, Forebrain Modulation of the Periaqueductal Gray). Some of the supraspinal regions involved in descending modulation include the hypothalamus, amygdala, insula, anterior cingulate cortex, and orbitofrontal cortex. These brain areas have direct or indirect connections with the periaqueductal gray and rostral ventromedial medulla, brain stem regions that play a critical role in brain-to-spinal cord modulation of afferent nociception within the spinal cord dorsal horn. However, the nociceptive signal and pain perception can undergo modulation at the supraspinal level also via supraspinal circuits. Therefore, these supraspinal regions and their connections to the spinal cord provide a means by which stress can modulate nociception and pain experience.

### Characteristics

The relationship between stress and pain is bidirectional; therefore, the next sections will cover each direction of influence.

### The Influence of Stress on Pain

#### Stress-Induced Modulation of Pain

The effect of stress on pain is complex because in some circumstances stress can inhibit pain (i.e., hypoalgesia), whereas in other circumstances it can enhance pain (i.e., hyperalgesia). Based on a review of the literature, Rhudy and Meagher (2001) proposed that the effect of stress on pain may be determined by the type of stressor. Specifically, when a stressor is severe and threat is imminent, an intense emotional state akin to fear is produced which leads to hypoalgesia. A classic example of stress-induced hypoalgesia is the soldier in the midst of battle who does not realize they have suffered a serious injury. Most of the research on stress-induced hypoalgesia comes from animal studies which find that direct exposure to a severe stressor (e.g., electric shock, forced swim in cold water, food restriction, restraint, social isolation/conflict, exposure to a predator) or exposure to stimuli that had been previously paired with a severe stressor (e.g., an environment in which shock was presented) leads to a reduction in pain-related behavior in the animal (Butler and Finn 2009). However, exposure to severe stressors (e.g., shock, a cue paired with shock, mental arithmetic combined with noise, spider exposure in spider phobics, combat video exposure in persons with posttraumatic stress disorder) also produces hypoalgesia in humans (Butler and Finn 2009). From an evolutionary perspective, stress-induced hypoalgesia is adaptive because active fight or flight is necessary when there is an imminent threat, and tending to a painful injury could interfere with the success of fight or flight behaviors (Bolles and Fanselow 1980).

A number of physiological mechanisms have been implicated in stress-induced hypoalgesia (Butler and Finn 2009). The brain regions of particular importance are the hypothalamus, amygdala, periaqueductal gray, and brain stem (i.e., rostroventral medulla, parabrachial nucleus, nucleus of the solitary tract). As noted in the earlier section on pain modulation, higher forebrain regions have connections with the brain stem, which in turn have projections to the spinal cord that can inhibit afferent nociceptive input at spinal levels. Therefore, these circuits are involved in stress-induced hypoalgesia. Some stress-induced hypoalgesia is mediated by endogenous opioid peptides (Watkins and Mayer 1986). For example, beta-endorphin is released by the pituitary during stress-evoked activation of the HPA axis. However, other forms of stress-induced hypoalgesia are mediated by non-opioid compounds (e.g., endogenous cannabinoids, GABA, oxytocin, adenosine, glycine, vasopressin) and some are dependent on stress hormones (e.g., ACTH) and activation of the HPA axis (Butler and Finn 2009). Monoamines, such as dopamine, serotonin, and norepinephrine, are also likely to play a role in stress-induced hypoalgesia, but may also contribute to some
forms of stress-induced hyperalgesia (Butler and Finn 2009).

In contrast to stress-induced hypoalgesia, Rhudy and Meagher (2001) propose that when a stressor is mild or is likely to occur sometime in the future, then a less intense emotional state akin to anxiety is produced, which leads to hyperalgesia. Stress-induced hyperalgesia is also evolutionarily adaptive because in the absence of an imminent threat, hyperalgesia would promote hypervigilance to somatic threats and such hypervigilance may help prevent injuries. Furthermore, if an injury had already occurred, stress-induced hyperalgesia would promote wound tending and other recuperative behaviors (Walters 1994). Stress-induced hyperalgesia has been studied using a variety of mild-to-moderate stressors in animals (e.g., mild electric shocks, changes in environmental temperature, holding by nape of neck, novel environments, vibration) (Imbe et al. 2006), as well as humans (e.g., pictures of threatening scenes, threatening mental imagery, stressful interview, light paired with mild shock, threat of shock, brief noise bursts, unpleasant odors) (Naliboff and Rhudy 2009). The neurocircuitry involved with stress-induced hyperalgesia is similar to that of stress-induced hypoalgesia, with the difference being that different receptor subtypes are involved (Butler and Finn 2009; Imbe et al. 2006).

Given that hyperalgesia and hypoalgesia are subserved by similar neurocircuits, it is not surprising that stress can activate inhibitory and facilitatory mechanisms simultaneously (Crown et al. 2004). This means that the net effect on pain is determined by which process predominates (inhibitory vs. facilitatory). So, if inhibitory mechanisms get depleted or become habituated in some way, then stress-induced facilitatory mechanisms would dominate, thus causing hyperalgesia (Bruehl et al. 2009). Interestingly, evidence suggests that many chronic pain states are associated with depleted inhibitory mechanisms, so there is very little evidence of stress-induced hypoalgesia in chronic pain (Naliboff and Rhudy 2009). As a result, stress-induced hyperalgesia may be one factor that contributes to the initiation and/or maintenance of chronic pain.

Stress-Related Disorders and Pain

Various psychological conditions co-occur with pain disorders and the relationship may be maintained by stress and concomitant emotional factors (Klossika et al. 2006). For example, chronic pain is often comorbid with depression, and depressed patients prone to high anxiety report greater pain, perhaps due to the fact that increased anxiety exacerbates pain experience (Romano and Turner 1985). Zautra et al. (2007) found that rheumatoid arthritis (RA) patients who had experienced multiple depressive episodes had greater pain and exhibited greater stress-induced hyperalgesia. Posttraumatic stress disorder (PTSD) and chronic pain also co-occur and the two may be maintained by the stress caused by both pain and trauma, which in turn leads to attentional biases, anxiety sensitivity, avoidance, anxiety, and cognitive demand (Sharp and Harvey 2001). Comorbidity between borderline personality disorder (BPD) and chronic pain has also been identified, and the link between the two may be due to problems with emotion/stress regulation mechanisms (Sansone et al. 2001).

Early Life Stressors and Pain

Some evidence suggests that early life stress can influence pain processing. For example, animals exposed to prenatal stress or neonate animals exposed to maternal separation are less capable of engaging pain inhibitory mechanisms later in life (Butler and Finn 2009). Further, early life stress is associated with long-term changes in the pain system, which in turn is associated with increased prevalence of human chronic pain such as irritable bowel syndrome and fibromyalgia (Al-Chaer and Weaver 2009). In a prospective longitudinal study, McBeth and colleagues (2007) found that HPA axis dysfunction, specifically high levels of cortisol post-dexamethasone, low levels of morning cortisol, and high levels of evening cortisol, was associated with an increased risk of developing chronic widespread pain. Furthermore, in a large sample of men and women, Anda et al. (2010) found that frequent
headaches in adulthood were associated with adverse childhood experiences (e.g., emotional or physical abuse) in a dose-response manner. Therefore, early life stress may have long-lasting effects that promote chronic pain in adulthood.

**Stress, Immune Function, and Pain**

The immune system plays an important role in protecting the body from invading bacteria, viruses, and foreign substances. Exposure to stressors influences immune function, but the direction of influence depends on timing and the type of stressor. Immediately following an acute stressor, immune activity is generally enhanced. This is adaptive as it allows the immune system to prepare itself for fighting off infection in areas that require it most. However, if the stressor is prolonged or repetitive, the immune system is unable to return to baseline and instead lapses into immunosuppression (Sapolsky 2004). Ultimately, prolonged suppression of the immune system can lead to the development of immunological disease and alterations in pain modulation. In fact, many autoimmune diseases (e.g., lupus erythematosis, rheumatoid arthritis, inflammatory bowel disease) are associated with persistent pain. Some of these effects are due to the release of chemical mediators such as cytokines, substance P, prostaglandins, bradykinin, chemokines, and nerve growth factor. For example, studies have shown that stress increases the production of cytokines (Moons et al. 2010) and that cytokines can increase pain and sickness behaviors by acting at spinal and supraspinal sites (including the hypothalamus) (Watkins et al. 2007). Cortisol release can act as an immunosuppressant by decreasing circulating levels of leukocytes, natural killer cell activity, and cytokines (Zeller et al. 1996). These chemicals are released after the onset of tissue destruction and inflammation and can impact the nervous system both peripherally and centrally. Although they are responsible for preventing and eliminating infection, these chemical mediators can also directly elicit pain through the activation of nociceptors (Rittner et al. 2009) (Fig. 1).

**The Influence of Pain on Stress**

**Pain and Stress**

As noted in earlier sections, incoming pain signals can directly activate the HPA and HSAM to evoke stress responses. Thus, pain can directly evoke stress. In chronic pain patients, not only can a lack of proper outlets for coping with stressful situations lead to the exacerbation of pain, but the consequences of chronic pain (e.g., feelings of threat/loss of social relations, depression, interpersonal conflict, disability, isolation) can amplify stress responses (Zautra et al. 1999). Therefore, pain can affect stress via multiple pathways.

**Chronic Pain and Stress-Related Disorders**

Chronic pain is associated with increased risk for stress-related disorders. This is not surprising as (1) both nociceptive and affective pathways overlap and (2) neurotransmitters such as norepinephrine, serotonin, and dopamine are associated with pain and emotion. Severity plays an important role in development of stress-related disorders, and as pain transitions from acute to chronic, stress/emotional factors play a more dominant role in its maintenance. For example, Sternbach et al. (1973) examined the psychological profiles of patients with low back pain and found that those with chronic pain demonstrated higher rates of psychopathology when compared to patients with acute pain. As noted earlier, depression is also commonly associated with chronic pain, with epidemiological studies reporting a prevalence rate ranging from 16% to 50% in pain patients (Romano and Turner 1985). Anxiety disorders, substance abuse, and personality disorders often co-occur with chronic pain. For example, a study by Kroenke et al. (1994) found that as the rate of physical symptoms increase in pain patients, so does the likelihood of anxiety or depression.

**Pain, Immunity, and Stress**

The stress of pain can also alter the immune system. For example, persistent pain has been shown to increase tumor growth and diminish wound healing, and when relief from pain occurs, this has been found to improve immune
functioning and wound healing (Page and Ben-Eliyahu 1997).

Chronic Pain and Quality of Life

The impact of chronic pain on quality of life is significant. Patients with chronic pain generally report diminished life satisfaction, greater disability, and decreased psychological, physical, and social well-being. The distress associated with chronic pain can be substantial and can lead to decreased occupational productivity, depression, loss of physical conditioning, fatigue, memory impairment, and social isolation.

Although a relationship exists between chronic pain and quality of life, studies have found this relationship to be fairly complex and mediated by several psychosocial and sociodemographic factors such as depression, social and physical functioning, fatigue, health perceptions, and stress-related symptoms (Wahl et al. 2009).

Therefore, chronic pain may not be directly related to quality of life, but instead may be mediated by multiple factors including stress.

References


quality of life: A study of the general Norwegian population. *Quality of Life Research, 18*(8), 971–980.


Stress and Pain,

Fig. 1  Diagram of the routes of communication between the brain and immune system, including the HPA axis, sympathetic nervous system, and cytokine feedback to the brain (from Webster et al. 2002)