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Pain in Times of Stress

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Abstract

Stress modulates pain perception, resulting in either stress-induced analgesia or stress-induced hyperalgesia, as reported in both animal and human studies. The responses to stress include neural, endocrine, and behavioural changes, and built-in coping strategies are in place to address stressors. Peculiar to humans are additional factors that modulate pain that are experienced in times of stress, notably psychological factors that potentially influence the directionality of pain perception.

Keywords: *stress, pain, analgesia, hyperalgesia, neuroimaging*

Introduction

From the time of conception, stress is present in human life (1). 'Stress' is defined as a state of disharmony or threatened homeostasis (2). Stress can be due to either physical or psychological stressors and it is followed initially by a response specific to the stressor (3). As the stress increases, the response takes on a more stereotypical nature, termed the 'General Adaptation Syndrome' (4). The sequelae of stress include neural, endocrine and behavioural responses. The neural response is activation of the sympathetic nervous system, resulting in release of epinephrine and norepinephrine (5), whereas the endocrine response involves stimulation of the hypothalamic-pituitary-adrenal (HPA) axis (6). The behavioural responses include increases in pain threshold, changes in locomotor activity and body temperature, and catalepsy (7). The neural and endocrine responses to stress can be summed up by the stress system.

The Stress System

The stress system is made up of central and peripheral components (3). The central components are located in the hypothalamus and brainstem, and they include (a) the parvocellular neurons that secrete corticotropin-releasing hormone (CRH), (b) arginine vasopressin (AVP) neurons of the paraventricular nuclei (PVN) of the hypothalamus, (c) CRH neurons of the paragigantocellular and parabrachial nuclei of the medulla and the locus caeruleus (LC), and (d) other mostly noradrenergic (norepinephrine, NE) cell groups in the medulla and pons (LC-NE system). The peripheral components include the peripheral limbs of the HPA axis and the efferent sympathetic adrenomedullary system (2).

The central components of the stress system interact with three higher brain control areas, namely (1) the mesocortical or mesolimbic system (affect and anticipatory phenomena), (2) the amygdala and hippocampus complex (propagation and termination of stress system activity), and (3) the arcuate nucleus (the setting of pain sensation) (3).

Activation of the stress system brings about various changes in body systems, including increased secretion of hypothalamic beta-endorphin and other proopiomelanocortin-derived peptides, such as adrenocorticotrophic hormone (ACTH), which reciprocally inhibits stress system activity, resulting in analgesia (8,9).

Coping Strategies to Stress

The body has built-in mechanisms to address stress. The term 'allostasis' means the process of maintaining stability (homeostasis) by active means, whereas 'allostatic load' means the wear and tear the body and brain undergo to achieve allostasis (10). Persistence of stress over time will deplete the body's resources, resulting in an increased allostatic load and eventually ending in disease or death.

Animals and humans display distinct coping strategies when faced with different types of stress. These coping mechanisms are mediated by neural substrates within the periaqueductal grey (PAG; 11). The PAG circuitry is organised into distinct

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longitudinal columns that function to coordinate somatomotor, autonomic, and behavioural reactions to different types of stress. The lateral column subserves escapable or controllable physical stressors, such as superficial pain. The dorsolateral column functions in reactions to psychological stressors, such as unconditioned stress or fear. Both of these columns are involved in active coping reactions, i.e., confrontational defensive or escape reactions. This is accompanied by hypertension, tachycardia, and analgesia. The third column is the ventrolateral column, which is activated when faced with an inescapable physical stressor, such as deep pain and opioid withdrawal, and psychological stressors in the form of conditioned stress or fear.

Involvement of the ventrolateral column results in a passive-coping reaction, such as quiescence and hyporeactivity, and is accompanied by hypotension, bradycardia, and analgesia (11). The dorsolateral and lateral PAG evoke nonopioid-mediated analgesia, whereas the ventrolateral PAG evokes opioid-mediated analgesia. Stressors, however, often combine physical and psychological elements, thus activating multiple PAG neuronal columns (12).

Parameters of Stress

Stress level can be determined using psychological as well as neuroendocrine measurements. The Symptoms of Stress Inventory (SOSI) (13) was designed to measure physical, psychological, and behavioural responses to stressful situations. The subject is asked to rate the frequency with which they experience stress-related symptoms on a 5-point scale ranging from never to frequently during the past week. Other measures include the Perceived Stress Scale (PSS) and the Life Events Stress Scale (14). The distress level may be measured using the Likert Scale, which ranges from 1 (not at all distressed) to 10 (extremely distressed).

The neuroendocrine measurements of stress levels include systolic and diastolic blood pressure, heart rate, salivary cortisol concentration, and salivary alpha-amylase activity (15–21).

Several psychological and psychosocial stressors have been utilised in studies of stress in humans. The Trier Social Stress Test (22), a public speaking and mental arithmetic stressor, and adaptations of this test (23,24) are widely used in studies of stress in humans (25,26). It has been shown that this stressor induces a strong stress response both by subjective report and physiological measures.

The Stress Appraisal Measure (SAM) is a measure of anticipation of stress (27). Grillon et al (28) used a similar speech presentation and mental arithmetic paradigm as the social stressor. Takai et al (16) showed a video of corneal surgery to induce psychological stress. The Montreal Imaging Stress Task, an adaptation of the Trier Social Stress Test, is used in functional imaging studies to investigate the processing of psychological stress in the human brain (24). It is derived from the Trier Mental Challenge Test and consists of a series of mental arithmetic tasks together with social evaluative threat components. Negative feedback in combination with a challenging cognitive task, such as mental arithmetic or public speaking as used in the Trier Social Stress Test (22), have been shown to be highly effective in eliciting strong stress responses. The combined cognitive challenge induces a strong stress response on both the subjective and physiological levels.

Neuroimaging in Stress and Pain Studies

Imaging provides a leap forward in stress (29) and pain studies (30). The advent of functional magnetic resonance imaging (fMRI) has made possible the study of human cognition by analysing brain activations (31). In pain studies, fMRI enables brain imaging during pain-intensity-related haemodynamic changes (32), as well as the modulation of pain by various psychological (33,34) and pharmacological interventions (35–37).

Wang et al. (38) used arterial spin-labelling perfusion MRI to measure cerebral blood flow changes associated with mild to moderate stress induced by psychological stress. Perfusion MRI is ideal for imaging a sustained behavioural state (e.g., stress) involving functions of deep brain structures because of its excellent reproducibility over long-term periods and minimal sensitivity to magnetic field inhomogeneity effects. Psychological stress induced by mental arithmetic tasks causes increased activation in the right ventral prefrontal cortex and left insula/putamen area (38). The ventromedial prefrontal cortex, along with the lateral orbitofrontal cortex and the amygdala, are associated with emotional processing (39), whereas the right prefrontal cortex is associated with negative affect (40). These activations are accompanied by increases in heart rate, salivary cortisol and perceived stress levels.

In a PET study, task-related increases in extracellular dopamine levels were observed

in the ventral striatum of individuals who mentally performed arithmetic computations in the Montreal Imaging Stress Task (24). fMRI findings in the same study revealed activations in the visual association cortices, angular cortex, sensory cortex, motor cortex, thalamus and caudate nucleus during the task performance. Performing mental arithmetic in the absence of stress resulted in activation of the posterior cingulate, angular, motor and visual association cortices. The main effects of stress were later shown to be activations in the left premotor area, the medial left prefrontal cortex, and bilaterally in the area of the cingulum/white matter (41). Apart from the activations, the psychosocial stress also caused deactivation of limbic system components including the hippocampus, hypothalamus, medio-orbitofrontal cortex, and anterior cingulate cortex. The presence of stress was determined by measuring salivary cortisol. This finding corresponds to the study reported by Niddam et al. (42) in which suppressed hippocampal activity was observed in patients with chronic pain (myofascial pain syndrome) when they were stimulated in a hypersensitive myofascial trigger point, reflecting stress-related changes in relation to chronic pain as a physical and emotional stressor. These findings suggest that a reduction in limbic system activity is essential for the initiation of the stress response (41).

Psychological/cognitive tasks used as stressors in imaging studies usually serve as a distraction to divert the subject's attention from the perception of pain. In these studies, both the task and the pain stimuli are applied at the same time, hence the effects are mainly due to attention focused on the stressor rather than the pain. Petrovic et al. (43) used cold pressor pain during an attention-demanding maze task and demonstrated decreased activity in the somatosensory association areas and the periaqueductal grey that was accompanied by lower ratings of pain and increased activation in the orbitofrontal cortex. Using the counting Stroop test as the distractor and applying noxious thermal heat, Bantick et al. (44) showed lowered activation in the pain matrix (thalamus, insula, cognitive division of the ACC) and increased activation in the affective division of the ACC and the orbitofrontal cortex. Using the colour-word Stroop test and heat pain, Valet et al. (45) demonstrated reduced activation in pain-related areas and increased activation in the cingulofrontal cortex, periaqueductal grey, and posterior thalamus.

It has been shown that anxiety exacerbates pain through activation in the hippocampus (33), which has led to suggesting ways to reduce pain by disengaging the hippocampus during potentially painful clinical procedures. A study using positron emission tomography (PET) showed that psychological stress in humans causes mesolimbic dopamine release (46). Using pain as the stressor, another PET study showed that basal ganglia dopaminergic activity is involved in pain processing, as well as emotional processing of the pain stimulus (47). Nigrostriatal D2 dopamine receptor activity was related to the sensory aspect of pain, whereas mesolimbic D2/D3 dopamine receptor activity was related to negative affect and fear. This finding outlines the regions involved in the physical and emotional responses to pain-related stress in humans.

Yilmaz et al. (48) performed an fMRI study to investigate the neural correlates of stress-induced analgesia (SIA) in humans. This study used mental arithmetic as the cognitive stressor, white noise as an additional distressing element and mechanical pressure as the pain stimulus. Subject participation was rewarded with monetary remuneration. An adequate stress response was elicited with this study design that was evidenced by physiological changes. The results showed that the analgesia (as indexed by increased pain tolerance from pre to post-stress) correlated with the BOLD response for the post versus pre-stress contrast in the rostral ACC and right SI. Correlations for the differences in pain unpleasantness perceived with the pre and post-stress using the BOLD contrast were significant in the dorsal ACC.

Directionality of Stress Effects on Pain Response

A crucial factor for the occurrence of SIA and stress-induced hyperalgesia (SIH) in humans is the influence of psychological and cognitive elements on stress and pain processing, which will in turn determine the outcome of the pain response. Pain experience in humans involves sensory-discriminative, motivational-affective, and cognitive components (49). Table 1 summarises the human studies on the effects of stress on pain behaviour.

Whether a human subjected to stress will exhibit analgesia or hyperalgesia is relatively subjective compared to the experience of animals and is dependent on the psychological effects that the stressor exerts on the individual's emotions. Emotion modulates pain through an interaction of valence (pleasant-unpleasant) and arousal (calm-excited) (50). The valence-by-arousal interaction

Table 1: Human studies on stress effects on pain behaviour

Stressor	Pain test	Pain behaviour observation	Reference
Foot shock	Flexion reflex	SIA	60, 61
Perceived coping inefficacy in a mathematical task	Cold pressor test	SIA Blocked by naloxone	62
Exposure of spider phobics to spiders	Electrical stimuli	SIA	63
Giving a speech about a recent anger arousing experience	Thermal pain stimuli	SIA only in women with low mean arterial pressure	64
Mental arithmetic	Cold pressor test	SIH	65
Fear induction by exposure to electrical shock Anxiety induction by threat of shock	Radiant heat	SIA SIH	51
Cold water immersion	Thermal CO2 laser	SIA	66
20-minute Stroop test	Capsaicin	SIA in men SIH in women	59
Anticipation of pain with visual cue presentation	Random and intermittent noxious stimuli	SIH	33
Mental arithmetic plus noise	Electrical stimuli	SIA	67
Public speaking	Cold pressor test	SIA	68
Speech task	Cold pressor test	No significant difference in intensity but increased post-pain negatice affectivity	69
Trier Social Stress Test	Tourniquet test (ischaemic pain) Cold pressor test Thermal pain stimuli	SIA – in men only No SIA SIA in women only (unpleasantness rating only)	25
External control of noxious stimuli	Electrical stimuli	SIH	70
Logical task using sequence of symbols with time pressure Emotional stress – pictures and audio of physical violence	Pin-prick	SIH – increased VAS score. SIH – increased VAS score.	58
Interview and serial subtraction	Cold pressor test	SIH	71
Anticipation of painful stimuli with presentation	Thermal pain stimuli	SIH	72
Metyrapone-induced hypocortisolism	Mechanical pain stimuli	SIH	73
Mental arithmetic plus white noise	Mechanical pressure	SIA	48
Induction of hypoglycaemic state	Thermal pain stimuli	SIH	74
Psychosocial stress test	Thermal pain stimuli	SIH	75

SIA – stress-induced analgesia.
SIH – stress-induced hyperalgesia.

determines the directionality of the stressor on the pain response. A negatively valenced emotion with low to moderate arousal evokes anxiety and enhances pain, whereas one with high arousal, such as fear, reduces pain (51). Conversely, a positively valenced emotion always reduces pain, as long as minimal arousal is achieved.

How the stressor is perceived by the individual is in turn determined by the personality of the individual. A person prone to catastrophising may find a stressor negatively affecting his or her emotions. Studies have shown that women have a higher predilection for catastrophising (52), although other studies did not find significant differences between men and women (53,54). Animal studies have shown that oestrogen enhances pain sensitivity (55), and women smokers with low oestrogen levels exhibit lower pain perception (25). Studies examining pain and differences between the sexes revealed that women are more sensitive to threat-related stimuli and experience more negative affect than men, leading to an increased pain perception (50).

One oft-quoted early example of the interaction between pain and stress is the observation by Dr. Henry Beecher (56) of soldiers wounded in battle who needed less analgesic than civilians suffering equivalent injuries. This observation suggests that the amount of pain felt by a person is determined by how the person perceives the pain. The soldiers injured in battle were better able to address their pain because of their acceptance of injuries as being part and parcel of being in battle, and they are relieved that their injuries do not lead to death. The civilians, on the other hand, treat their injuries as a major tragedy, hence their heightened pain perception. This suggests that the amount of pain perceived by a person is governed not only by the amount of tissue injury present but also by emotional and psychological factors. The injury caused more distress to the civilians than to the soldiers, and this leads to more pain, i.e., hyperalgesia.

The motivation-decision model by Fields (57), states that analgesia may either be the avoidance of a bigger threat than pain or the anticipation of reward. In the face of menace, such as threat of a predator, attending to the dangerous situation takes precedence over attending to the pain, hence analgesia. Likewise, in situations where a reward can be gained, the motivation for reward attenuates the sensation of pain, resulting in analgesia.

In the study reported by Stoeter et al (58), subjects performed a cognitive task and were subjected to an emotional stressor before they received a pin-prick pain stimulus. Pain ratings after both stressors were increased, indicating hyperalgesia. However, brain activation during pain stimuli after cognitive stress was reduced, whereas activations after emotional stressors were increased.

The pain stimulus used to inflict pain is another factor that determines the directionality of the effect that stress exerts on the pain response. An inescapable pain stimulus, such as capsaicin, causes more distress than an acute pain stimulus, such as thermal heat pain. In the study by Logan et al (59), stress due to a 20 minutes Stroop test followed by capsaicin injection enhanced pain intensity in women only, whereas men exhibited reduced pain.

Stress-induced Analgesia

SIA is well documented in animal studies, and various manipulations have been employed to produce analgesia to pain stimulation, namely stress in the form of footshock (76), swimming (77), novel environment (78) or immobilization (79). Induction of SIA in laboratory animals showed that low levels of stress facilitated learning and responding, whereas high levels disrupted responding (80). Psychological stress and stress resulting from loud noise increased anxiety-like (81) and depressive-like behaviour (82, 83) but decreased working memory functioning (84, 83) in rats.

Animal studies of SIA are considered a model of the anecdotal reports of reduced pain sensation in humans during extreme situations (85). Extensive research on animal responses to stress and pain stimulation is not always an acceptable predictive model for SIA in humans. SIA is not easy to quantify in humans, given the obvious limitations involved in subjecting humans to stress and pain. Furthermore, the animal model is capable of distinguishing the specific pain modalities (86), whereas human pain includes overlapping aspects of specific types of pain. Clearly, the factor that separates the responses observed in animals and those in humans is the higher level cognitive processing that occurs in the human brain, and these in turn are determined by various factors, namely past experiences, learning, and memory moulded by the plasticity of the central nervous system (87).

Early human studies on SIA by Willer used the expectation of noxious stimulation, i.e., a noxious footshock given at 7 to 8 times the pain threshold as the stressor, which inhibited the nociceptive flexion reflex (60, 61). Several other

studies have shown evidence of stress-induced analgesia using noxious heat (88) and physical stress (89).

In later studies, however, other means have been used to expose subjects to stress and have included manipulations of psychological (90) and cognitive stress (62). Bandura et al (62) used perceived coping inefficacy in a mathematical task to elicit SIA in a cold pressor test. The analgesia was blocked by naloxone, suggesting the opioidergic system meditated the response. For a review of the underlying mechanisms of SIA, please see Butler and Finn (91).

Stress-induced hyperalgesia

Animal studies have shown that acute stress, such as inescapable holding, (92) and chronic stress, such as repeated swim stress (93,94), actually induced hyperalgesia instead of analgesia. Chronic stress has been shown to attenuate dopaminergic activity in the nucleus accumbens, resulting in hyperalgesia (95). Rats exposed to chronic unavoidable stress exhibited a decrease in dopaminergic tone in the shell of the nucleus accumbens (96). The decrease in dopaminergic tone lasted up to 14 days after the stress exposure. Rats submitted to chronic stress also displayed hyperalgesia for up to 28 days (95). Chronic stress also caused decreased morphine sensitivity, suggesting that the opioidergic systems were modified. Quintero et al (93) demonstrated that hyperalgesia due to an inescapable subchronic stress is resulted from diminished central 5-HT activity. The underlying mechanisms for SIH are reviewed in Jennings et al (97).

A study in children with recurrent abdominal pain showed that stress reduced the pain threshold instead of causing analgesia (71). Chronic pain patients have reported enhanced pain during stress (42). Stress has been shown to exacerbate pain in gastro-oesophageal reflux patients (98). Modulation of oesophageal perception by anxiety, stress and depression cause patients to perceive low intensity oesophageal stimuli as being painful. Studies performed in fibromyalgia patients showed that stress causes an increase in musculoskeletal pain (99). Excessive stress beyond the control of the individual may be followed by dysphoria, reduced functioning (100) and eventually psychiatric (101) or somatic disease (3). Other findings show that prolonged stress causes dysfunction of the HPA axis, causing metabolic derangement that subsequently leads to obesity and other metabolic syndromes, such as Type 2 diabetes and atherosclerosis (102). Stress-reducing strategies have also been used to alleviate pain in patients undergoing surgery (103).

Conclusion

Stress itself is subjective, with different emotions contributing to its manifestations, often with conflicting effects on pain perception as evidenced by the analgesic and hyperalgesic responses. The stress system does not function alone; the genetic and psychological makeup of a person, experience and environmental factors all contribute to the response to pain. The interactions among these factors subsequently result in the sequelae of survival, disease or even death.

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Conflict of Interests

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Authors' Contributions

None.

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