Chapter 17

WHY PAIN RELIEF IS IMPORTANT: THE PHYSIOLOGICAL RESPONSE

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INTRODUCTION

One of the main reasons we treat pain is to relieve suffering; it is one of our four bioethical principals—beneficence— and one of the most critical aspects of care for a patient. Treatment will improve patients' quality of life, their ability to work, and their physical and emotional functioning. Another reason to treat pain is because it activates complex neurohumoral, neuroendocrine, immune, and psychological responses, known together as the stress response. If severe and prolonged, pain can have deleterious effects on patient rehabilitation and outcome. The adverse physiological effects are legion and the magnitude and duration of the response is related to that of the stimulus.[1] Most experimental data are from studies with combined tissue trauma and the resultant pain. However, data has been collected about pain in the absence of injury using electrical stimulation, which still shows the stress response.[2] Effective pain management can significantly impact upon the physiological response to injury. This chapter will review the mechanisms of the initial pain response and discuss how acute pain management improves long-term outcomes.

THE INITIAL STRESS RESPONSE

The initial tissue trauma or pain elicits the neuroendocrine response with activation of the hypothalamic-pituitary-adrenal axis. This activation is driven by the limbic input to the hypothalamus via the paraventricular nucleus. The pituitary gland secretes adrenocorticotropin (ACTH), growth hormone, vasopressin, prolactin, and endorphins, while stimulation of the sympathetic nervous system increases plasma catecholamines, resulting in tachycardia and hypertension. Sympathetic stimulation also activates the renin-angiotensin system with subsequent increases in plasma aldosterone. This hormonal soup leads to the catabolic process, as mentioned, in proportion to the initial stimulus.

The main responses can be broadly classified into metabolic, inflammatory, hyperalgesic, cardiovascular, respiratory, coagulation, and immune function. The metabolic response can be further divided into protein catabolism, lipolysis, hyperglycemia, and changes in water and electrolyte balance (Figure 17-1).

Key Hormones Released

Cortisol is a glucocorticoid released from the adrenal cortex in response to ACTH secretion. In severe pain and trauma, the normal feedback mechanisms fail, so persistently high levels of cortisol are produced. Cortisol has far-reaching effects resulting in protein catabolism, lipolysis, and carbohydrate metabolism; it promotes gluconeogenesis and has insulin-suppressive effects. It also has antiinflammatory and immune suppressant effects by inhibiting the accumulation of macrophages and neutrophils; it also reduces inflammatory mediators and affects water and electrolyte balance.

Growth hormone released from the anterior pituitary has hyperglycemic effects due to its glycogenolytic and lipolytic actions, as well as effects causing insulin resistance. Growth hormone also has anabolic effects with regard to protein, although these effects are not large enough to counter the massive overall catabolic effects of the stress response.

The effect of insulin, or indeed its lack of effect, contributes to the stress response. Insulin is an anabolic hormone that leads to glucose storage and utilization. In the stress response its release is initially inhibited by the effects of catecholamines, but subsequently resistance to its effects develops due to failure of cellular response.

Increased arginine vasopressin—antidiuretic hormone—release and increased sympathetic activity with catecholamine release occur with the stress response. The responses to these substances are detailed in other parts of this chapter. (There are also increased secretions of other hormones such as glucagon, prolactin, and endorphins, which have less important effects and are outside the scope of this book.)

Metabolic Responses

Protein Catabolism

The initial response includes a net catabolism of protein into amino acids for gluconeogenesis. The process is driven by increased catecholamines, cortisol, glucagon, and interleukins. As the stress response produces an accelerated protein breakdown as well as an inadequate reaction or reduction in total protein synthesis, a negative nitrogen balance results. Skeletal muscle protein is mainly affected, and the loss of up to 0.5 kg per day of lean muscle mass may result in decreased muscle strength, delayed wound healing, and reduced immune function.[3] Albumin production is also reduced, affecting the maintenance of the extracellular volume and leading to edema.

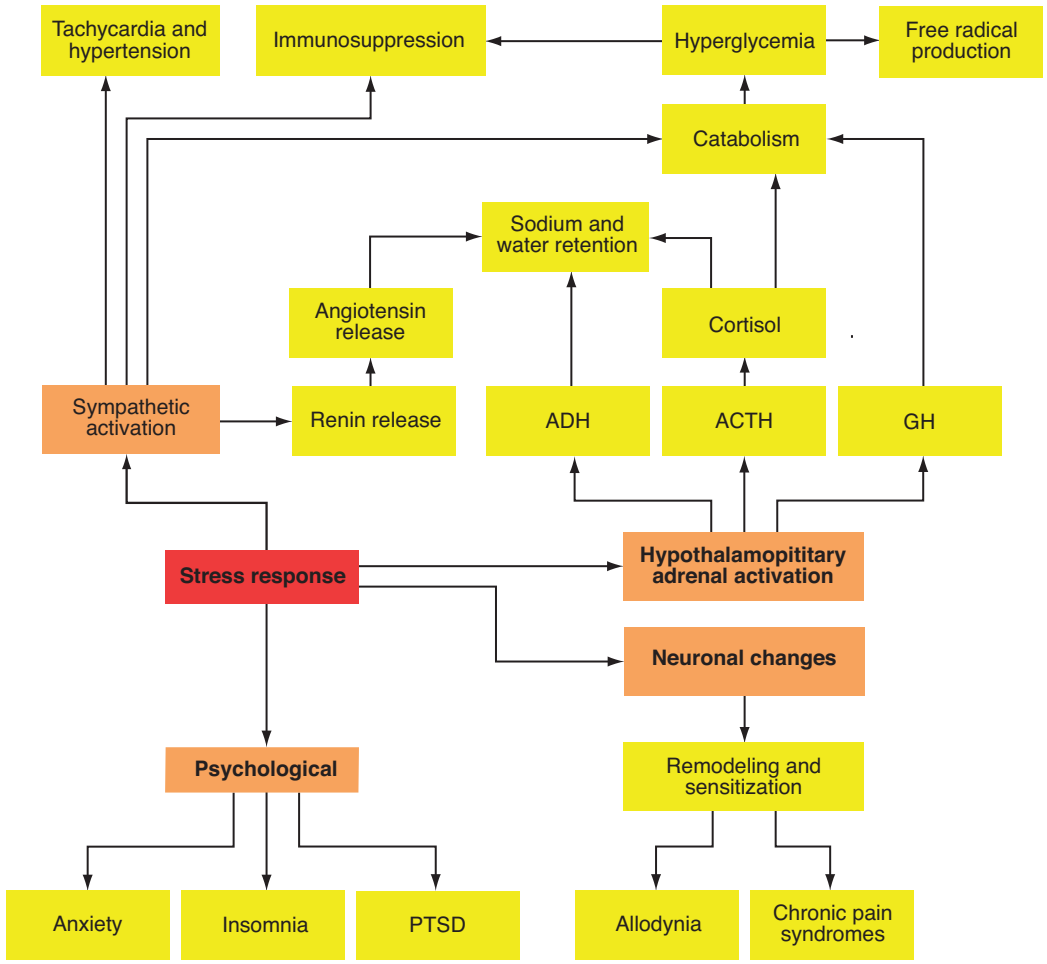

Figure 17-1. Diagram showing various components of the stress response.
ACTH: adrenocorticotropin; ADH: antidiuretic hormone; GH: growth hormone; PTSD: posttraumatic stress disorder

Lipolysis

Lipolysis, with resultant increases in free fatty acids and glycerol, is due to increased levels of circulating catecholamines, glucagon, cortisol, and growth hormones and reduced amounts of insulin. The higher levels of free fatty acids can have a negative inotropic effect, increasing myocardial oxygen consumption—with the possibility of ischemic damage—and possibly increasing free radical production.[4] Glycerol is a gluconeogenic substrate that further contributes to the hyperglycemic state.

Carbohydrate Metabolism

Catecholamine, glucagon, and cortisol also produce hyperglycemia, which is potentiated by an initial lack of insulin secretion followed by insulin resistance. The catecholamines and cortisol promote glycogenolysis and gluconeogenesis. The excess circulating glucose results in protein glycosylation and increased free radical production. The increased protein glycosylation, among other effects, reduces immunoglobulin function, thus increasing risk of infection. The raised levels of free radicals lead to increased mitochondrial dysfunction and eventual cell death. Glucose concentrations greater than 11.1 mmol/L are associated with impaired wound healing, increased infection rates, increased hospital length of stay, and increased mortality.[5]

Water and Electrolyte Balance

Renin is released from the juxtaglomerular cells of the kidneys in response to sympathetic stimulation; this results in angiotensin I being converted to angiotensin II. The increased angiotensin II stimulates the adrenal cortex to release aldosterone, which leads to

increased sodium reabsorption and water retention from the distal convoluted tubules. Arginine vasopressin release from the posterior pituitary results in water retention and potassium excretion. These effects are increased by the mineralocorticoid activities of cortisol, producing water retention, potassium excretion, and sodium reabsorption.

System Responses

Cardiovascular

Pain activates the sympathetic nervous system, which may increase the myocardial oxygen demand through its chronotropic, inotropic, and hypertensive effects. The increased sympathetic demand can also reduce oxygen supply by causing coronary artery vasoconstriction. These two factors along with the hypercoagulable state greatly increase the chance of myocardial ischemia.

Respiratory

Hypoxemia and other pulmonary complications can result from pain. Pain can reduce functional respiratory capacity, producing atelectasis and ventilation–perfusion mismatch. Atelectasis, caused by the inability to take deep breaths, and reduced effective coughing due to pain increase the risk of chest infections.

Immune Function

As previously discussed, immune function is reduced by persistently high levels of not only cortisol but also catecholamines, and to a lesser extent growth hormone and prolactin. These hormones reduce natural killer cell activity, antibody production, and lymphocyte proliferation.[6]

Neurological Systems

Chronic pain is common following trauma and surgery and is a major cause of ongoing patient morbidity.[7] Changes can occur in peripheral nerves, the spinal cord, higher pain centers, or the sympathetic nervous system. Inflammation at the site of injury can result in increased levels of mediators such as bradykinin, monoamines, prostaglandins, and leukotrienes. These chemicals sensitize afferent C fibers, resulting in a reduced threshold for firing. There is also an increase in the numbers of nociceptors. Central sensitization occurs at the dorsal horn, where there is an exaggerated response to C fiber and A-β input. "Wind-up" can occur due to activation of *N*-methyl D-aspartate receptors, leading to chronic pain syndromes and a cycle of pain difficult to treat. Models of the pathophysiology of pain suggest that within minutes of injury, neuronal expression of new genes occurs. This is the initial phase of neuronal remodeling and sensitization.

Early analgesia can prevent or reverse this cascade. Preemptive analgesia may not be possible for trauma patients, although early epidural insertion or continuous peripheral nerve block can often be used. Aggressive analgesia following trauma may reduce both acute and chronic pain by reducing both peripheral sensitization from the injury and central sensitization with its subsequent wind-up.

PSYCHOLOGICAL RESPONSES

Failure to relieve acute pain is associated with undesirable psychological changes, including anxiety, insomnia, and feelings of helplessness and loss of autonomy. Failure to treat acute pain can increase the incidence of chronic pain and posttraumatic stress disorder (PTSD), which are far more difficult to treat.[8] It has been found that pain scores following traumatic injury within the first 48 hour period are strongly associated with the development of PTSD. Indeed, an observational study suggested that the use of morphine in the initial trauma resuscitation can significantly reduce the development of PTSD.[9] Results of studies on the use of substances such as benzodiazepines and β-blocking agents have been inconsistent.[10,11]

Pain is subjective. It has a variable correlation with the extent of tissue injury and is multifactorial in nature. The psychological response is affected not only by adequacy of pain control but also by the patient's psychological resilience, previous pain experiences, culture, anxiety levels, mood, and preparedness. It is also dependent on situational factors. Engel's biopsychosocial illustration of pain demonstrates that pain cannot always be treated purely by analgesic administration because of the complex interaction between the three components.[12] Beecher noted that military patients with similar injuries had lower analgesic requirements compared to their civilian counterparts.[13] This difference was thought to be because the injury was associated with evacuation from the war zone and rehabilitation in a safe environment including families and support for family members. In the civilian setting, on the other hand, recovery from trauma was associated with decreased earning power and an uncertain future with potential for social hardship.

SUMMARY AND PATIENT OUTCOMES

It can be inferred from the physiological response to pain and trauma that adequate acute pain management is essential to modulate the potent stress response. Pain management will aid in attenuation of the multiorgan dysfunction, the catabolic state, hypercoagulability, resultant chronic pain syndromes, and the psychological effects of uncontrolled pain. Rapid effective pain relief at the point of injury is needed to reduce the neuronal remodeling and sensitization that occurs within 20 minutes of the initial trauma. In the chaotic combat environment, pain relief reduces casualties' physiological stress and facilitates evacuation. Analgesia must then be continued throughout the care and rehabilitation process.[14] It has been found that adequate neuroaxial analgesia can reduce protein catabolism, cortisol levels, and hyperglycemia while improving immune function.[6,15]

Studies show a good correlation between inadequate analgesia and the catabolic state, pulmonary complications, immunosuppression, and thromboembolic events. There is also moderate correlation with PTSD, chronic pain states, and mortality.[16]

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