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. 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. 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. Albumin production is also reduced, affecting the maintenance of the extracellular volume and leading to edema.
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 vasopres- 
sin 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–perfu-
sion 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 re-
duced 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.

Neurological Systems

Chronic pain is common following trauma and 
surgery and is a major cause of ongoing patient mor-
bidity. 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 leuk-
okrienes. 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 syn-
dromes 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 remodel-
ing and sensitization.

Early analgesia can prevent or reverse this cascade. 
Preemptive analgesia may not be possible for trauma 
patients, although early epidural insertion or contin-
uous peripheral nerve block can often be used. Aggres-
sive 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 un-
derirable psychological changes, including anxiety, 
insomnia, and feelings of helplessness and loss of 
avonmty. Failure to treat acute pain can increase the 
incidence of chronic pain and posttraumatic stress 
disorder (PTSD), which are far more difficult to treat. 
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. Results of studies 
on the use of substances such as benzodiazepines and 
β-blocking agents have been inconsistent.

Pain is subjective. It has a variable correlation with 
the extent of tissue injury and is multifactorial in na-
ture. 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 biopsyc-
chosocial illustration of pain demonstrates that pain 
cannot always be treated purely by analgesic admin-
istration because of the complex interaction between 
the three components. Beecher noted that military 
patients with similar injuries had lower analgesic re-
quirements compared to their civilian counterparts. 
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 associ-
ated 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. It has been found that adequate neuroaxial analgesia can reduce protein catabolism, cortisol levels, and hyperglycemia while improving immune function. 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.

REFERENCES


