The Nature and Physiology of Pain

Introduction

Pain is a concept that is difficult to define. It is often described as an unpleasant sensation localized to a part of the body; and as a sensory and emotional experience associated with actual or potential tissue damage. In its broadest sense, pain is many things: a physiological response to a physical event; a perception; and a subjective experience, in which physical, emotional, and situational factors play key roles.

Pain can be caused by a heterogeneous group of diseases and conditions, such as malignancy, arthritis, back pain, and simple bruising. This multitude of underlying conditions adds to the complexity of the issues involved in the diagnosis and management of pain.

To the suffering patient, pain can be an excruciating experience. Although a symptom resulting from an underlying condition, rather than being a disease in itself, pain can worsen the causative condition and cam even become the major problem. Persistent pain can disable the patient, leading to severe physical, psychological, and economic problems. If inadequately treated, pain can result in unnecessary medical and surgical procedures, depression, substance abuse, **narcotic (opioid)** habituation, or suicide. (Physicians tend to use the term *narcotic* rather than *opioid*, although opioid is probably the more accurate term. *Opiate* refers specifically to a drug obtained from the seed capsule of the opium poppy, but the term is sometimes used interchangeably with *opioid*.)

For the physician called upon to treat pain, the diagnosis and management of the underlying condition — and the pain itself — can be among the most difficult challenges in medical practice. In addition to the physical aspects of pain, which, in themselves, are difficult enough to manage, the physician may need to help patients cope with emotional problems related to pain: fear, discouragement, and emotional distress. Patients with chronic or recurrent pain can be hostile and demanding of the physician's time.

They may develop unreasonable demands and expectations, and become increasingly dependent. Yet the relief these patients seek may be difficult or even impossible for the physician to provide. This situation is difficult for the physician, trained to comfort and heal, to accept.

From the patient's perspective, pain is one of life's most unpleasant experiences. Severe acute pain typically is accompanied by emotional disturbance or extreme mental anguish, intensifying the patient's suffering. Chronic pain, often accompanied by depression, may cause loss of appetite, and weight loss; or increased appetite and weight gain; sleep disturbances; and exhaustion. Various forms of mental distress — fear, worry, anxiety, and apprehension — are common components of chronic pain. Often, patients become frustrated, and angry at the physician for not doing more to resolve their pain.

The human and socioeconomic tolls of pain in the U.S. are enormous:

O An estimated 80 million Americans — one third of the population — suffer from chronic pain.[1]

O About 433 million work days are lost annually because of pain.[1]

O Approximately $8 billion is spent annually on prescription and over-the-counter pain relievers.[2]

O About $70 billion is spent each year on medical needs, lost working days, and compensation related to chronic pain.[3]

O More than 50 million trauma injuries involving pain are reported each year.[4]

This chapter of the program discusses the physiology of pain, including the structures involved in pain perception; and how the nervous system and the body respond to pain.

Learning Objectives

When you have finished this chapter, you should be able to:

1. Identify the characteristics of pain.

2. Briefly describe the events that occur in the peripheral nervous system when tissue is injured.

3. Name the nerve pathways that carry a pain impulse from the peripheral nervous system to the central nervous system.

4. Identify the areas in the brain involved in the responses to pain impulses.

5. Identify the characteristics of the inflammatory response.

6. Identify the characteristics of prostaglandins and leukotrienes.

7. Briefly define the terms *sensitization* and *hyperalgesia*.

8. Identify the characteristics of pain modulation.

9. Identify the structures and substances involved in pain modulation pathways.

The Physiology of Pain

When tissue is injured, the brain receives a pain stimulus and perceives pain. The structures involved in pain perception are:

O the **sensory nerves** of the **peripheral nervous system (PNS)**, which detect stimuli such as pain and initiate electrical impulses

O the brain and spinal cord, which make up the **central nervous system (CNS)**, where the electrical impulses are received, interpreted, and acted upon

The major divisions of the PNS and CNS are shown and defined below.

(INSERT VISUAL: THE NERVOUS SYSTEM)

Nerves and Neurotransmitters

The Role of Nerves

When tissue is cut, burned, or otherwise injured, the endings of specialized sensory nerves, called **nociceptors**, detect a painful stimulus. The stimulus causes changes in the normal flow of **ions** into and out of the **neuron** (conducting cell of the nervous system).

As shown below, each neuron has a long process, known as an axon, that extends far from the cell body.

(INSERT VISUAL: ADAPTATION OF A GENERALIZED NEURON)

The changes in flow of ions into and out of the neuron create electrical impulses that travel along the nerve process to the next nerve cell.

The Role of Neurotransmitters

Because individual neurons are separated by a gap, called a **synapse**, the electrical impulses are not passed directly from one neuron to another. Instead, chemical "messengers," called **neurotransmitters**, carry the electrical information across the synapse to the next neuron.

In this way, impulses are carried, in just a fraction of a second, from the peripheral nerves to the **spinal nerves**, spinal cord, and ultimately to the brain, where they are interpreted and acted upon.

How the Nervous System Responds to Pain

Reflex Actions

Reflex responses to pain, such as those that occur when the hand is yanked away from a hot surface, are carried out by the spinal cord.

These reflex actions do not involve thought processes such as interpreting information.

Perception

Thought processes *do* occur in the "gray matter" of the brain, known as the **cerebral cortex**. The cortex is a layer of gray matter that forms the surface of the cerebrum. Within the gray matter, the nerve impulse is interpreted as pain of a specific type, degree, and location. In response, the brain produces physical, emotional, mental, and behavioral responses that are unique to each person.

How the Body Responds to Pain

Some of the body's responses to pain actually enhance pain; others

relieve pain.

Pain-Enhancing Actions

Inflammation

Inflammation is a normal, protective response. When it occurs inappropriately, however, as in rheumatoid arthritis, or is prolonged or overwhelming, it can be destructive.

Physiologically, inflammation is a localized, *protective* response to cell damage. In what is known as the **inflammatory response**, the body reacts to tissue injury or destruction, as follows:

O Blood flow to and from the area increases

O The affected area is "walled off" until healing occurs

O Large numbers of protective cells migrate to the area and devour damaged tissues

The term "walling off" the affected area means that fibrous clots are formed in the involved tissues, virtually sealing off the tissue spaces and fluids. This protective response stops the flow of fluid within the tissue spaces, delaying the spread of toxic products or bacteria to nearby, healthy tissues.

Symptoms that accompany inflammation include heat, redness, swelling, impaired function, and pain. Swelling intensifies the pain, for it creates pressure in the tissues.

Normally, deep tissues and organs are not very sensitive to painful stimuli. But when inflammation is present, as in appendicitis, they can become extremely sensitive. It is thought that these deep tissues and organs contain silent nociceptors, which can be activated by inflammatory mediators. This activation is believed to give rise to the severe pain that is characteristic of appendicitis and other inflammatory disorders.

Among the tissue products involved in the inflammatory response are **prostaglandins**, **leukotrienes**, and other mediators of pain and inflammation. These pain mediators, released by injured cells, play a role in initiating electrical impulses in local nerve endings. The electrical impulses produce pain impulses that are sent to the spinal cord and brain. The figure below summarizes the mechanisms by which injury results in inflammation and pain.

(INSERT VISUAL: ADAPTATION OF MECHANISM OF INFLAMMATION AND PAIN)

Sensitization

Sensitization can occur whenever damaged or inflamed tissues are subjected to intense, repeated, or prolonged pain stimuli. Sensitization lowers the level of pain stimulus necessary to activate nociceptors.

In sensitized tissues, even minor stimuli can cause pain, a condition known as **hyperalgesia**. Normally innocuous stimuli become painful, and the pain resulting from normally painful stimuli is intensified.

Pain Modulation

In a process known as **modulation**, the response to pain can vary markedly in different situations and in different individuals. These variations in the response to pain are thought to involve complex nerve pathways that modulate pain impulses within the CNS and PNS.

Examples of the modulation process include the following:

O To some people, minor injuries are almost unbearably painful.

O Athletes and military personnel may continue to function despite painful injuries or severe wounds that would incapacitate most people.

O The *expectation* of pain can produce pain when no painful physical stimulus exists, such as fear of dental pain during a routine cleaning.

O The *expectation* of obtaining pain relief can relieve pain. For example, taking a **placebo** can have an **analgesic** effect, even though the placebo has no pharmacologic effect.

Note that, as shown in these examples and discussed below, pain modulation can reduce pain or enhance it.

Within the nerve pathways believed to be involved in pain modulation are **opioid receptors** and **endogenous opioids,** consisting of neurotransmitters, such as **endorphins** and **enkephalins**; and pain-inhibiting and pain-facilitating neurons. Their roles are described below.

Pain-Relieving Mechanism

Prolonged fear or pain are thought to activate the **pain-modulating network**, resulting in the release of endogenous opioids. For example, these opioids appear to be released following surgical procedures, or after a placebo is administered in a clinical trial designed to evaluate the effectiveness of pain medications.

The pain-relieving mechanism occurs in three steps:

1. endogenous opioids are released

2. the endogenous opioids bind to opioid receptors

3. the binding inhibits the ability of receiving nerves to carry pain impulses

The analgesic effects of endogenous opioids are similar to those produced by morphine.

Although the existence of the pain-modulating network has not been proven, it has been found that diseases involving the structures believed to be part of the modulating network diminish the analgesic effects of morphine and other opioids.

Pain-Enhancing Mechanism

The modulating nerve pathways described above are thought to be involved in creating or increasing pain by activating pain-facilitating neurons. The pathways may also play an important role when psychological factors contribute to pain, and when pain is induced by suggestion.

In summary:

Pain management is among the most difficult challenges encountered in modern medical practice.

Pain is:

O a physiologic response
O a perception
O a subjective experience

The body's responses to pain are complex, and involve the CNS and the PNS:

O When tissue is injured, nerves of the peripheral nervous system send electrical impulses to the central nervous system.

O The spinal cord initiates immediate reflex actions.

O In the cerebral cortex (gray matter), nerve impulses are interpreted as pain and acted upon.

The body responds to pain through the following actions:

O pain-enhancing:

—inflammation: a protective response that can, under certain conditions, enhance pain

— sensitization: a response in which a relatively low level of pain can activate pain receptors, once tissues have been subjected to intense, repeated, or prolonged pain

o pain-relieving:

—release of endogenous opioids

In the physiological process known as pain modulation:

O The body reduces or intensifies pain impulses, enhancing or reducing pain.

O Complex nerve pathways within the CNS and PNS are thought to be involved.