Physiology and Pathophysiology of Pain

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Abstract

The production of pain and the biological responses to it are part of a highly integrated system which helps animals to react, respond and protect themselves from their environment. The pain system includes sensors, neural pathways and processing centers that are responsible for detecting, transmitting and actualizing the animals biological and behavioral responses to noxious events. The development of peripheral sensitization, central sensitization and permanent alterations in the way that animals process painful events are just some of the ways that animals protect themselves from their environment. Understanding the physiologic and pathophysiologic processes responsible for pain is essential to rational pain therapy.

Introduction

Pain serves an extremely important function warning of potential tissue damage and protecting the recipient from further injury, and as such is considered the "fifth clinical sign". Animal pain has been defined as, "an aversive feeling or sensation associated with actual or potential tissue damage" broadening the dictionary definition to include behavioral changes, neuroendocrine activation and the "stress" response.[1] The latter definition is the basis for why pain perception (nociception) is not considered to fully represent the pain experience and helps to explain the relationship between painful experiences and pain behaviors in animals. Nociception is the neurophysiological process whereby noxious mechanical, chemical or thermal stimuli are **transduced** into electrical signals (action potentials) by high threshold pain receptors (nociceptors) located on the peripheral terminals of very thin uninsulated or minimally insulated (myelinated) C and Ad nerve fibers, respectively. The electrical signals are subsequently **transmitted** to the superficial layers of the dorsal horn of the spinal cord, modified **modulated**, and **projected** to the brain **perception**. Physiologic or "ouch" pain is nociceptive pain that protects the recipient from tissue damage. Pathologic pain is produced by tissue or nerve damage and can be nociceptive (activation of high threshold nociceptors) or non-nociceptive (activation of low threshold sensory receptors).[2] Tissue damage and inflammation produce a wide variety of chemical mediators ("sensitizing soup") including prostaglandins, histamine, bradykinin, nerve growth factor, cytokines and chemokines. These chemical signals sensitize peripheral nerve terminals changing high threshold nociceptors to low threshold nociceptors and activating quiescent or "silent" receptors resulting in **peripheral sensitization** and hypersensitivity to nonpainful stimuli (zone of primary hyperalgesia). More severe tissue trauma or nerve damage produces electrical signals that continuously bombard dorsal horn neurons producing a cumulative effect and activation of alternate receptors on dorsal horn neurons, resulting in **central sensitization**. Central sensitization is responsible for a zone of secondary hyperalgesia and allodynia or the sensation of pain from noninjured tissue by nonnoxious stimuli.[2] Together these pathologic neurophysiological processes modify the molecular signaling processes in the spinal cord resulting in permanent alterations in how sensory inputs are processed (neuroplasticity), leading to chronic pain syndromes and associated behavioral modifications.

Physiologic Pain vs Pathologic Pain

Pain is produced by activation of functionally specialized Aδ and C nerve terminal receptors (nociceptors) which convert (transduce) harmful (noxious) thermal, mechanical and chemical stimuli into electrical signals that are transmitted to the central nervous system. The free nerve endings of these afferent pain processing fibers encode noxious stimuli depending upon the modality, intensity, duration and location of the stimulus. The intensity of the stimulus which produces pain is considerably greater than that required to elicit innocuous sensations, and is the most important factor determining the severity of pain and can be quantitatively defined by a stimulus intensity-response relationship similar to other sensations. In the absence of tissue damage pain is considered to be "physiologic" warning to the animal of potentially harmful stimuli. Pathologic pain occurs when tissues or nerves are damaged and has been "clinically" categorized as inflammatory or neuropathic.

Unlike physiologic pain, pathologic pain can be produced by stimulation of large myelinated Aβ nerve fibers which normally do not transmit painful sensations. Severe injuries and chronic pathologic pain states

can change (dynamic plasticity) intensity of the stimulus required to initiate pain (hypersensitivity). The development of tissue hypersensitivity (nociceptive sensitization) can be responsible for the development of increased sensitivity to noxious stimuli (hyperalgesia) and painful sensations arising from normally nonpainful stimuli (allodynia).

Peripheral Sensitization

Tissue damage and inflammation result in activation and release of intracellular components from damaged cells, inflammatory cells (lymphocytes, neutrophils, macrophages), and the primary nerve fiber itself. The local release and spread of ions (H^+, K^+), prostaglandins (PGE_2), bradykinin, cyclooxygenase, neurotrophic growth factors (NGFs) and cytokines (IL1, IL6, TNFα) sensitizes pain fibers to subsequent painful and nonpainful stimuli.[3] Mast cell degranulation increases the local concentration of 5-hydroxytryptamine (serotonin) and histamine. Together these substances produce a **"sensitizing soup"** which lowers the threshold of nociceptors and activates "silent" nociceptors (10-40% of total nociceptor population) amplifying the pain response. Local vasodilation, and plasma extravasation results in a further amplification of the inflammatory response and the spread of hypersensitivity to surrounding tissues (secondary hyperalgesia).

Central Sensitization

Central sensitization occurs when the cumulative effects of frequent (chronic) or severe peripheral nociceptor input releases excessive quantities of central nervous system nuerotransmiters (substance P, neurokinin A, BDNF), including glutamate which activates NMDA and other receptors, resulting in an increase in sensitization ("wind-up") of neurons in the dorsal horn of the spinal cord.[3] Sensitization of dorsal horn neurons can last for hours, and is believed to be responsible for pain outside the area of tissue injury (secondary hyperalgesia) and allodynia. Central sensitization is fundamentally different from peripheral sensitization in that it enables low-intensity stimuli to produce pain sensations. When pain is chronic it enables sensory fibers which normally transmit nonpainful stimuli (low threshold Ab fibers) to produce pain as a result of changes in sensory processing in the spinal cord. Central sensitization increases the responsiveness of dorsal horn neurons to sensory inputs (allodynia), expands receptive field and is believed to be responsible for the discomfort and agony produced by severe injury. Chronic pain is responsible for activity-dependent plasticity and long term structural changes (neuroplastic) within the central nervous system. The extension of central senstization from the spinal cord to the brain lead to the development or modification of memory patterns that are responsible for changes in animal behavior. Together the development of wind-up, central sensitization represents a continuum of the pain process, which exists as consequence of continuous, unrelenting and untreated pain which leads to stress and distress.

Stress and Distress

Stress is an adaptive pattern of behavioral, neural, endocrine, immune, hematological and metabolic changes directed toward the restoration of homeostasis. The stress response prepares the animal for an emergency reaction and fosters survival in circumstances of immediate threats (fight or flight). Acute pain is capable of producing a significant stress response by initiating activation of the sympathetic nervous system, secretion of glucocorticoids (primarily cortisol), hypermetabolism, sodium and water retention and altered carbohydrate and protein metabolism. Prolonged or severe stress eventually becomes maladaptive, producing distress and the activation of self-sustaining cascades of neural and endocrine responses that derail physiologic homeostasis. Prolonged stress impairs the animals ability to interact, learn and changes the animals behavioral phenotype.[1] Severe pain produces behavioral, auto-

Table 1. Activation and sensitization of nociceptors ("sensitizing soup").

Substance	Origin	Effect
Hydrogen ion	Damaged cells	Activation
Potassium ion	Damaged cells	Activation
Prostaglandins (PGE2)	Damaged cells	Sensitization
Leukotrienes	Damaged cells	Senistization
Bradykinin	Plasma	Activation
Serotonin	Platelets, mast cells	Activation
Histamine	Mast cells	Activation
Substance P	Sensory nerve endings	Sensitization
Nerve Growth Factor	Sensory nerve endings	Sensitization

nomic, neuroendocrine and immunologic responses that may result in "sickness syndrome", self-mutilation, immune incompetence and a poor quality of life potentially leading to gradual deterioration and death.

Current and Future Therapies

Rational treatment of pain requires an appreciation of its consequences, a fundamental understanding of the mechanisms which are responsible for its production and a practical appreciation of the analgesic drugs that are available (Figure 1). The clinical treatment of pain should consider the multiple mechanisms (mutilmodal therapy) responsible for its production and the value of administering analgesic therapies before pain is initiated (preemptive therapy).

References

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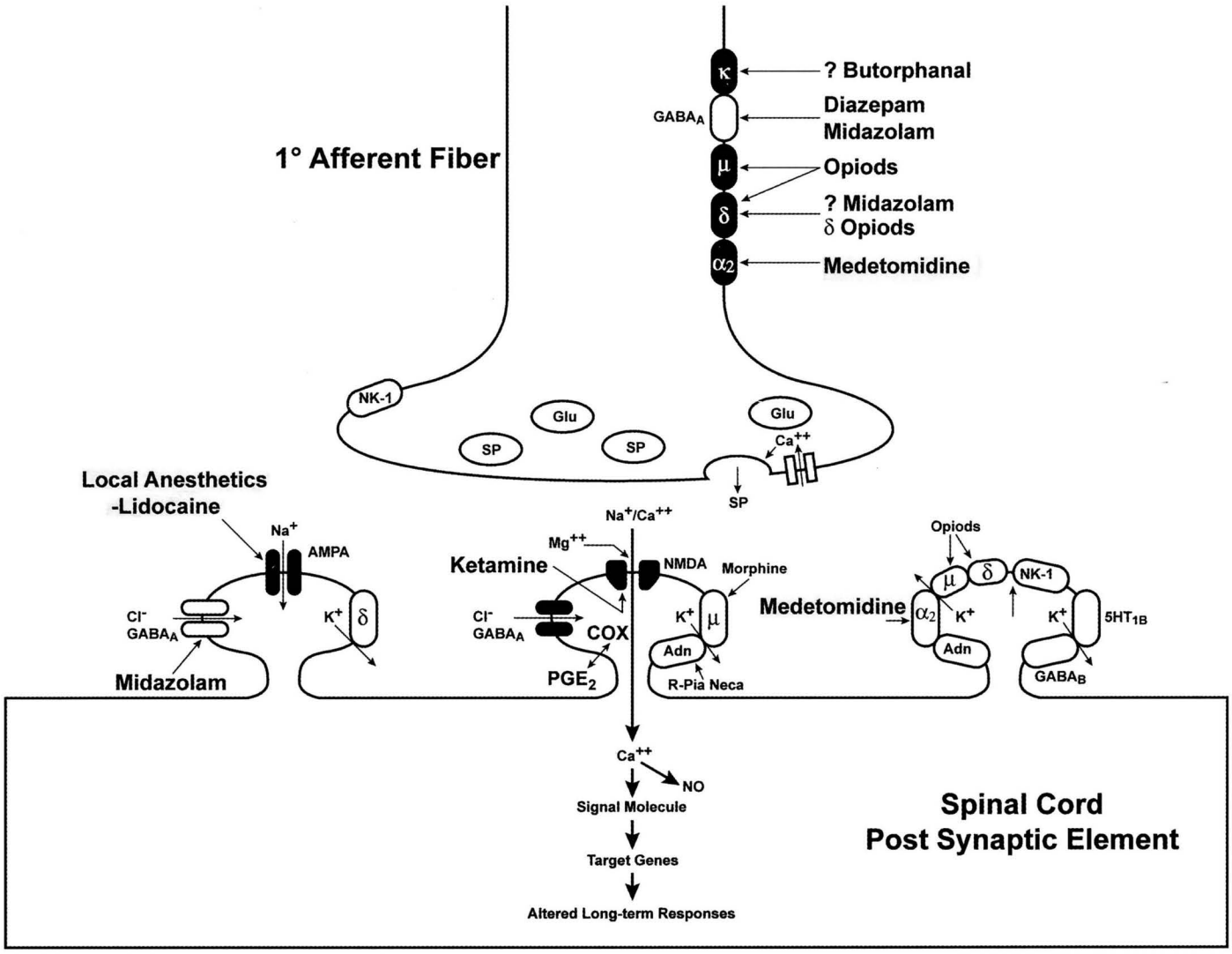
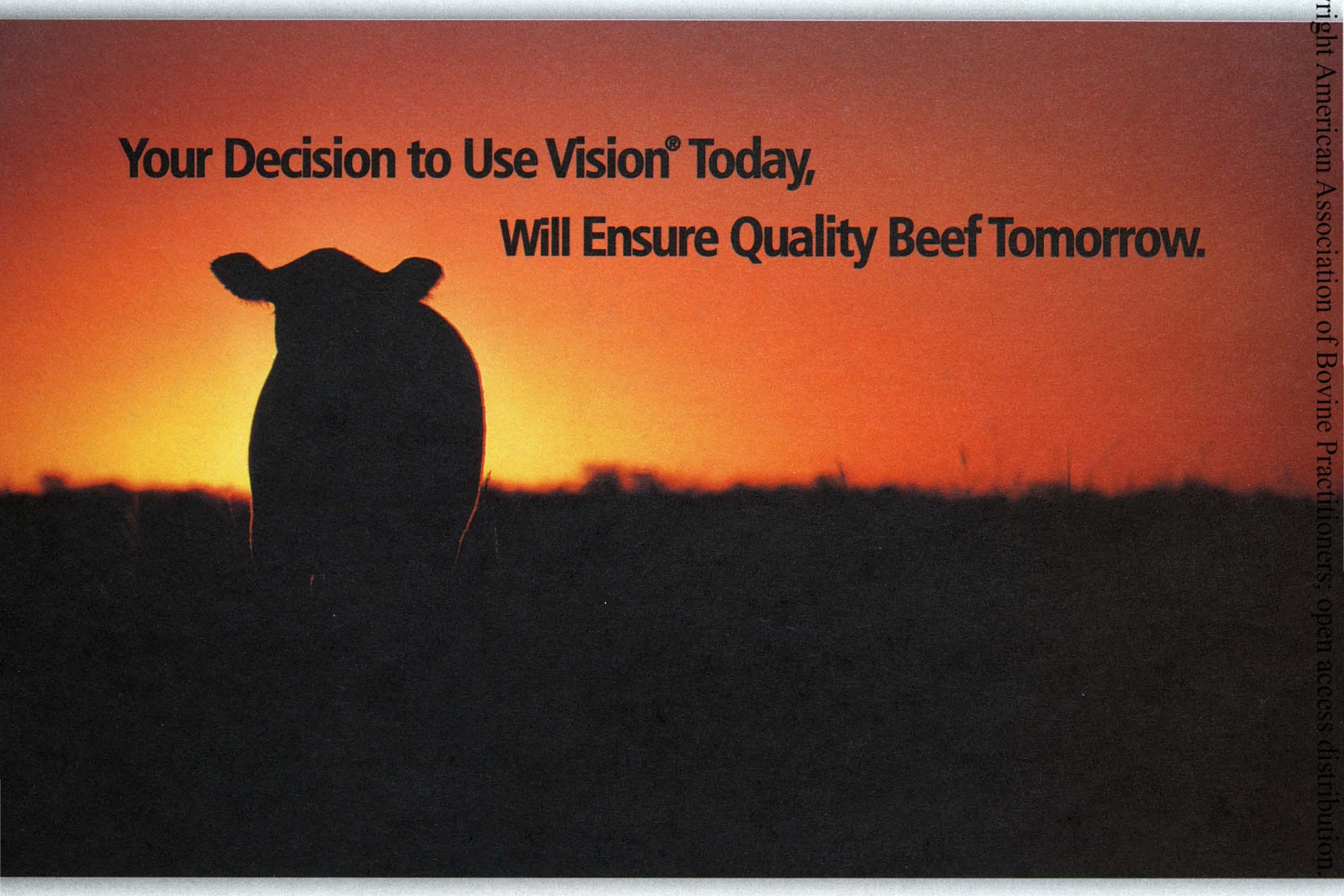


Figure 1. Drugs and receptor sites known to produce analgesia in animals.



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