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PAIN: NEUROPHYSIOLOGY AND EXPERIMENTAL EQUINE MODELS

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SUMMARY

Pain is a complex phenomenon which is both a sensory experience and a feeling state. Pain is a specific sensation which is mediated by certain types of neurons and pathways in both the peripheral and central nervous systems. The spinal cord is an important site of pain processing which can be influenced by drugs and other endogenous physiological processes.

Pain can be studied by both subjective and objective means. Several objective methods for measuring pain perception in the horse have been developed which include the radiant heat, thermal implant and balloon-induced colic models. While these models measure thresholds for cutaneous, deep somatic, and visceral pain, respectively, they are attended by substantial variability and limited reproducibility. An new method for measuring cutaneous pain perception in the horse using noxious thermal stimuli is described and its advantages over existing methods are discussed.

THE DEFINITION OF PAIN

Pain can be defined as a sensory experience which signals the destruction or threatened destruction of tissue. It may be convenient to think of this experience as a converging dichotomy of both sensation and feeling state, as shown in Figure 1. As a sensory event the perception of pain is useful in that it signals imminent tissue damage and initiates certain nocifensive reactions such as the flexor reflex. Autonomic responses are also elicited such as increases in heart rate and respiratory rhythm which help the organism execute the nocifensive reaction. These responses occur readily in both man and in the equine. As a feeling state, pain is characterized by unpleasantness or suffering which imparts an aversive quality. This aspect of the pain experience may be useful in that momentary suffering reinforces acquisition of aversive behavior. Thus, the stimulus which produced pain or the threat of pain can be used to control behavior, coerce action or obtain obedience.

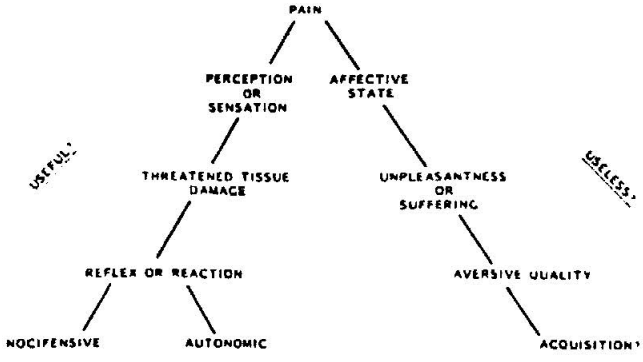

Fig. 1: The converging dichotomy of pain

Pain is also a symptom or sign of an underlying pathophysiological process to which the organism must attend. However, pain rapidly outlives its usefulness when it persists for prolonged periods in the absence of an acute stimulus. Persistant or chronic pain and the attendant suffering can cause great harm and alter the psychophysiology of the organism. Thus, pain can be viewed as an often necessary but undesirable condition (Bishop, 1980a,b; Beers, 1979).

THE NEUROPHYSIOLOGY OF PAIN

Pain is a specific sensation that is mediated by a distinct group of receptors and nerve fibers. It is a specific sensory modality that can be elicited independent of other sensations and selectively altered by drugs. Pain receptors or nociceptors are undifferentiated nerve endings that transduce noxious stimuli. They may be functionally categorized as unimodal nociceptors that respond principally to noxious mechanical stimuli and polymodal nociceptors that respond to chemical, mechanical and intense thermal stimuli. Polymodal nociceptors are associated with sensitization or hyperalgesia and are probably involved in inflammatory pain.

Pain is conducted by anatomically and functionally distinct nerve fibers. C-fibers are unmyelinated, fine diameter, slow conducting fibers. They mediate slow, burning pain and are thought to underlie suffering. A-delta fibers are fine myelinated afferents which mediate faster, sharp pain.

A variety of stimuli can elicit pain sensations. Among these are (1) mechanical deformation of tissue or underlying nerves, (2) heat or thermal stimuli in exess of 45 C, (3) a variety of endogenous chemical substances released by damaged tissue which include K^+, H^+, histamine, bradykinin, prostaglandins, and substance P, (4) tissue ischemia and (5) disease.

The first level of the sensory integration of pain and other modalities is the dorsal horn neuron of the spinal cord. This neuron receives inputs from sensory nerve fibers (or primary afferents), from descending pathways from the brain, and from other dorsal horn cells. These neurons are influenced by a variety of neurotransmitter substances and drugs that inhibit or enhance the activity of the neuron. Certain cells respond only to painful stimuli which are specifically suppressed by narcotics. In turn, the dorsal horn neuron outputs to other segments of the spinal cord and sends pain information rostrally toward the brain.

Pain processing occurs at various levels of the central nervous system (CNS). The spinal cord is the first sensory relay which ultimately integrates reflex behavior. Ascending information projects to the thalamus where the quality of the pain stimulus is discriminated. The thalamus then influences the brainstem, basal ganglia, limbic system, hypothalamus and the cortex. The brain stem mediates cardiopulmonary changes, while the hypothalamus elaborates homeostatic hormones in response to the stimulus. The basal ganglia "fine tunes" reflex behavior involved in the aversive response, while the limbic system processes the affective or emotional component. The cortex ultimately integrates and prioritizes the painful event with other cognitive processes (Eccles 1982; Zimmerman 1979; Bishop 1980a). On the descending limb, pain can be modified at the spinal cord level by certain brain stem systems. The periaqueductal gray and raphe nuclei, when activated naturally or by the narcotics, modulate, select and control pain input by releasing substances onto the spinal cord dorsal horn cell. Thus the quality and quantity of the pain information is altered before it ever reaches the conscious level. Endogenous opiate-like peptides have recently been discovered in a variety of species. These peptides are released during stress or painful events and exert analgesic effects in vivo (Benedetti 1979, Bishop 1980b; Eccles 1982).

EXPERIMENTAL MODELS OF EQUINE PAIN

Pain perception in the horse has been measured by a variety of subjective and objective methods. The subjective methods include: (1) digital pressure (Jones and Hamm, 1978) (2) needle probe (Kerr *et al.*, 1972) (3) hoof compression (Szabuniewicz & Szabuniewicz, 1975) and (4) clinical observation (Gideon, 1977). The objective methods include: (1) radiant heat (Pippi *et al.*, 1979 a, b), (2) thermode implantation (Pippi *et al.*, 1979 a, b) and (3) balloon-induced colic (Lowe, 1969; Pippi *et al.*, 1979 a,b). The majority of studies describing pain perception and its therapeutic modification employ subjective techniques. Pain is often scaled or scored based on clinical observations. This form of quantitation is inherently imprecise, varies among observers or within the same observer, and is subject to bias. Objective measures of pain, while more difficult to execute, are more reproducible, more readily quantifiable, and less variable. Objective studies of pain in the horse are few.

The ideal objective pain model should fulfill the following criteria: (1) the pain stimulus employed induces a clearly defined end point or threshold which can be quantitated, (2) the pain stimulus should elicit similar responses among all subjects and be administrable repeatedly to the same subject, (3) the pain stimulus produces minimal tissue damage so that repeated observations are not confounded, (4) the stimulus intensity must be measurable and adjustable to produce the desired response, (5) the stimulus is, in fact, painful, (6) pain is the only sensory modality elicited, (7) the model is sensitive enough to detect dose-related effects of analgesic substances. This list of criteria is similar to that described by earlier pain research in humans (Hardy *et al.*, 1940; Beecher, 1957).

Perhaps the most widely used method of measuring pain perception in man and animals is the radiant heat method originally described by Hardy *et al.*, (1940), and recently employed in the horse by Pippi and co-workers (1979 a,b). This method measures superficial or cutaneous pain threshold. The light obtained from a 1000 watt projector lamp is focused on an area of skin above the coronary band of the forelimb. The skin is blackened with lamp black prior to application of the light. Withdrawal of the affected limb activates an accelerometer which terminates the stimulus. Reaction time is measured and serves as an index of pain threshold. The advantages of this technique are that the stimulus selectively activates thermal nociceptors and is indeed painful. Reflex withdrawal of the affected limb is a readily observed nocifensive reaction with a clear end point. Thresholds are reproducible with the same subject and between subjects, and repeated measures can be made (e.g. skin temperature, lamp voltage or wattage, etc.). The limitations of this method are that acute noxious thermal stimuli do not reflect true pathological pain. Threshold to thermal pain may be quite different from visceral or deep pain especially regarding responses to analgesic drugs. Operant conditioning and tissue injury may be produced after repeated stimuli.

A slightly different method has been employed to study deep somatic pain in the horse (Pippi *et al.*, 1979 a,b). A heating element encased in a silastic tube is implanted on the midlateral periosteal surface of the radius and held in place by a bracket fabricated from Kirschner wire. Current is passed through the element which is then heated to a noxious temperature. An accelerometer attached to the forelimb terminates the stimulus when the limb is flexed and reaction time (threshold) is measured. Since deep, somatic pain is thought to arise from muscles, joints, periosteum, ligaments and underlying structures, this method seems to approximate such pain. However, this type of pain is poorly localized which probably contributes to the highly variable thresholds obtained. Since the response is slow and heat dissipation inherently limited, tissue damage may occur with repeated stimuli. The longevity of such a chronic implant is also questionable (Pippi *et al.*, 1979 a,b).

Yet another method has been employed to study visceral pain. This technique originally described by Lowe (1969) has been modified by Pippi and co-workers (1979a, b) and simulates colic pain. A plastic cannula is implanted in the caecum through which a rubber balloon is inserted. The balloon is then rapidly inflated to a predetermined pressure. The time elapsed between pressurization and initiation of colic-like movements of sufficient (arbitrarily measured) force represents the visceral pain threshold. It has been established that visceral sensations occur when the intestinal lumen is stretched. Receptors lining the mucusa and serosa signal changes in tension and shape of this organ. Pain is produced when distension is marked and prolonged. There is little doubt that distension of the hollow viscus occurs upon insertion and

inflation of the intraluminal balloon. However, the endpoint at which pain is produced is difficult to determine in nonhuman species. Do colic-like symptoms represent the acute pain phase or premonitory distension phase? Which colic-like movement is most reflective of true abdominal pain? Would a vocalization response be more accurate? These questions are not readily settled. Pippi *et al.*, (1979a, b) have reported a high degree of variability in the thresholds between determinations and among different subjects. However variable, this response can be influenced by analgesic drugs which have been employed in the treatment of equine colic.

THE RADIANT HEAT EVOKED SKIN TWITCH REFLEX

Recent studies from our laboratory made use of a radiant heat technique similar to that described by Pippi *et al.* (1979 a,b) for measuring cutaneous pain threshold. The light from a projector lamp was focused on the fetlock area and pain threshold was measured as the latency between onset of the light and limb flexion. Although this method was effective for the drugs studied, there are several limitations which precluded more extensive trials. As reported by Pippi *et al.*, (1979), we found that certain subjects became conditioned to the arrival of the light stimulus, thereby compromising the precision of the measurement. In addition, variability in latency occurred due to forelimb weight shifts prior to flexion. Spontaneous limb movement in some animals made baseline determinations difficult. Enhanced spontaneous limb movement, for example by narcotic drugs, would further confound such baseline or post-drug determinations. Stimulation of a large area of tissue was also required using this technique, increasing the potential for tissue damage. Subsequently, a modification of the heat lamp device was fabricated to circumvent the limitations described above. This device consists of a dual heat lamp which is attached by flexible gooseneck connectors to an abdominal girth (Figure II). This device is stabilized by a steel plate and surcingle and when mounted remains in a fixed position dorsal and caudal to the withers. One of the enclosed lamps consists of a projector bulb and condensing lens which focuses a beam of light to a fine point on the withers area (Figure III). Noxious thermal pain perception evokes a reflex contraction of the cutaneous trunci muscle. This skin twitch reflex then serves as the necessary endpoint for terminating the stimulus. The skin twitch reflex latency is a measure of cutaneous pain threshold. This response had been used for a number of years to measure dose-related analgesic effects of the narcotics in the dog (Martin and Jasinski, 1977). The second lamp assembly has a lower wattage bulb and no condensing lens. It provides a comparable source of light but no heat when illuminated.

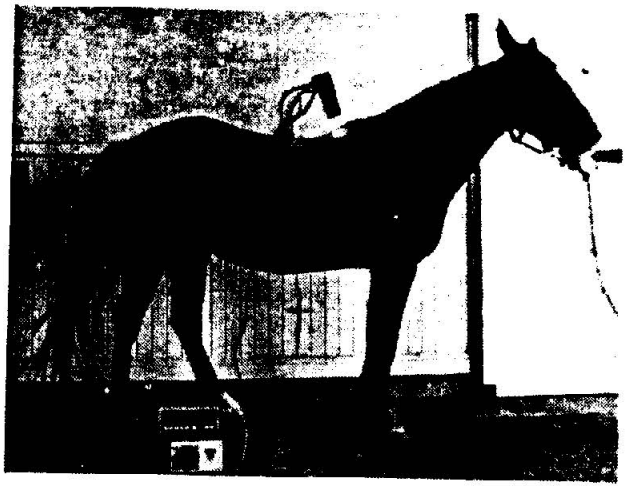

Fig. II: Experimental subject outfitted with heat projection lamp. The lamp assembly is attached to a steel plate and surcingle which is held in place by a girth around the abdomen. An electronic timer, voltage regulator and remote controller are shown at ground level.

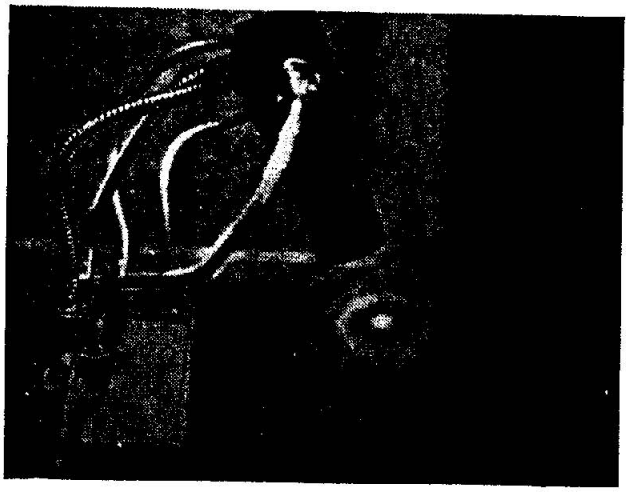

Fig. III: Close up of heat projection lamp. A beam of light (approx. 1.5 cm diameter) is shown focused on the withers just lateral to the midline.

The device provides several important advantages over existing noxious thermal heating instruments. First, the distance between the heat source and the skin is stable and is not influenced by spontaneous locomotor movements in the horse. Conditioned anticipatory responses to light cues are eliminated by randomizing the order of administration of the non-heat and heat producing light stimuli. A smaller more well-defined area of tissue is affected and the stimulus loci can be readily changed. The nociceptive endpoint is readily identifiable and reproducible. Lastly, this device is convenient to use and provides minimal hazard the the experimenter. This new technique for measuring cutaneous pain perception has not previously been described in the horse. It should provide a more precise, reproducible and sensitive means for assessing and comparing the efficacy of variety of classes of analgesic agents.

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FOOTNOTE

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