Scand. J. Lab. Anim. Sci. No. 4 . 1991 . Vol. 18

Physiology of pain mechanisms[1)]

by *Ralph L. Kitchell,* DVM, PhD, VMDhc,
Professor Emeritus of Veterinary Neuroscience, Department of Anatomy, School of Veterinary Medicine, University of California, Davis, California 95616-8732

Contrary to popular opinion pain is not a physical, nor physiological entity, but instead is a psychological event, a perception of the mind. The physiological events which lead to the perception of pain can all take place in an anesthetized animal, or a part to an animal, without the animal perceiving the stimulus (or event) as pain. Thusly, there are actually no "pain" stimuli, receptors, nerve impulses, pathways, centers, etc. even though these terms perpetuate in the literature. A pain stimulus is only that if it is perceived as pain. The proper term for stimuli leading to the perception of pain is to refer to them as "noxious" stimuli (*Sherrington* 1906). The correct term for the events leading to the perception of pain should be nociception or nociceptive events.

On the peripheral ends of nociceptive afferent fibres are specific receptors, called nociceptors, which respond to noxious stimuli. Neural activity generated by nociceptors are transmitted to the spinal cord or the brain stem, thalamus and the cerebral cortex for sensory processing. The processing involves a sensory-discrimination component and an affectional-motivational component. The sensory-discrimination processing of nociceptive nerve impulses appears to be very similar to the processing that occurs in other sensory systems such as visual, auditory, or mechanoreception systems. Nociception is the most effective system of any of the sensory systems for eliciting the arousal response via the motivational-affective component of the system. This component also elicits, in parallel with the sensory-discriminative component, both simple and complex motor and autonomic nervous system activity at various levels of the nervous system (spinal cord, brain stem, hypothalamus, and the forebrain). The final evaluation of the sensory inputs as pain includes discriminatory components such as location, intensity, duration and quality of the pain as well as the affective-motivational component which leads to emotional reactions such as anxiety, suffering, and depression.

Activation of nociceptors occurs when the noxious stimulation is of sufficient intensity to cross the **nociceptor threshold.** The activation of the nociceptors does not always lead to a perception of the stimulus as pain. When the intensity of the stimulation is gradually increased to the point that the stimulation is first perceived as pain, the **pain detection threshold** has been crossed. The pain detection threshold is approximately the same in man and animals (*Vierck* 1976, *Zimmermann* 1984, *Kitchell & Johnson* 1985). The maximum intensity of experimental pain that an individual (human or animal) will tolerate is referred to as the **pain tolerance threshold**. The difference between the pain detection threshold and the pain tolerance threshold is referred to as the pain sensitivity range. The pain tolerance threshold varies widely among individuals as well as among species. The pain tolerance threshold is greatly affected by motivation, stress, previous experience, cultural background and analgesics.

An important distinction should be made between nociceptive reflexes and pain perception. A reflex is an involuntary, purposeful and orderly response to a stimulus. A response, in neurological terminology, consists of willful movement of the body, or parts of the body. A response cannot be performed

1) For more complete discussion of animal pain please consult: *Kitchell & Johnson 1985, Kitchell* 1987, *Kitchell & Guinan* 1990.

without involvement of the somatosensory parts of the cerebral cortex. A decerebrate animal can give a reaction, but not a response. A nociceptive reflex can occur without perception of the stimulus which initiated the reflex as a painful stimulus. Pain perception in animals is indicated by voluntary actions of the animal in response to the stimulus, called a **pain response.** This consists of the animal turning its head toward the stimulus, alteration of the respiratory patterns, biting at the source of the stimulus, vocalization and other signs which indicate cortical participation in the aversive response. It is extremely difficult to determine the intensity of the stimulation based upon the animal's response to the application of the stimulus.

Pain in humans has been classified as acute or chronic dependent upon the duration of the pain. A pain is classified as a chronic pain if it exits more than 6 months. Chronic pain appears as separate syndromes quite distinct from acute pain.

The qualities of pain are related to the site of origin of the pain (Fig. 1). If the pain is initiated from stimulation of receptors located in the viscera of the body it is referred to as visceral pain and has different perceptual qualities than pain initiated from stimulation of other parts of the body, or somatic pain. Somatic pain is further subdivided into superficial pain, if it comes from the skin or subcutaneous tissues, and deep pain, if it comes from the deeper structures of the body wall. Pain associated with A delta fibers has a pricking quality whereas pain associated with C fibers produces a burning sensation. A delta fibers have been associated with the first, fast or initial pain (Fig. 2), which is described as the sharp, stabbing, well localized quality of superficial pain. The C fibers have been shown to be associated with the second, slow, or delayed pain which is described as the dull, burning, diffusely located quality of superficial pain. Not all A delta and C fibers are pain fibers. Some have receptors associated with them, called mechanoreceptors, which respond to non-noxious mechanical stimulation, other receptors, called thermoreceptors, respond to non-noxious cold and heat.

Nociceptive receptors and primary afferents

Skin or cutaneous nociceptors can be grouped into one of several classifications based on the types of stimuli they respond to. *Mechano-nociceptors* are activated by intense mechanical stimuli. They have conduction velocities of small myelinated fibers

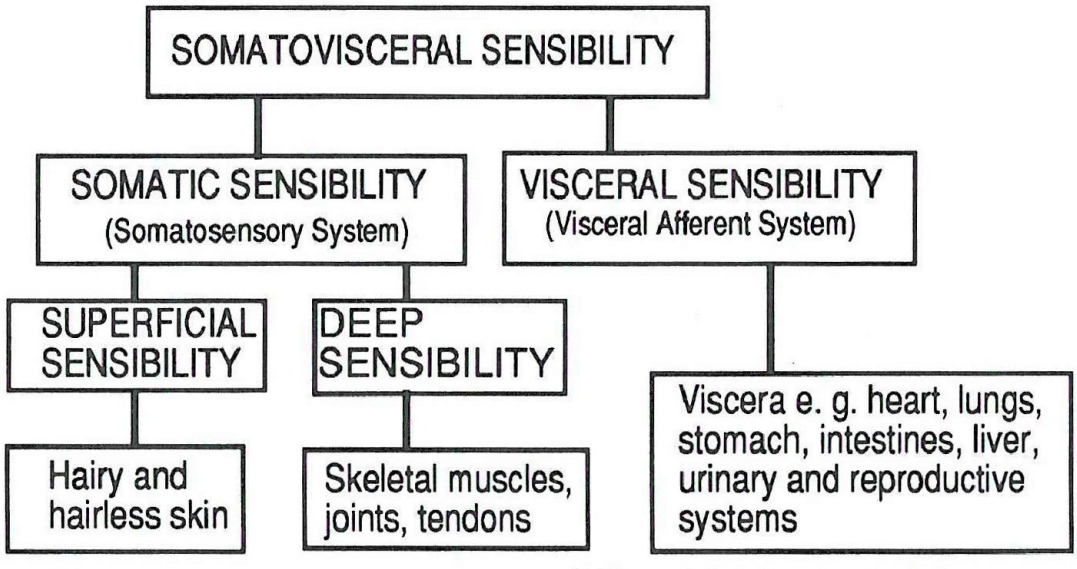

Figure 1. Components of somatosensory sensibility and their location in the body.

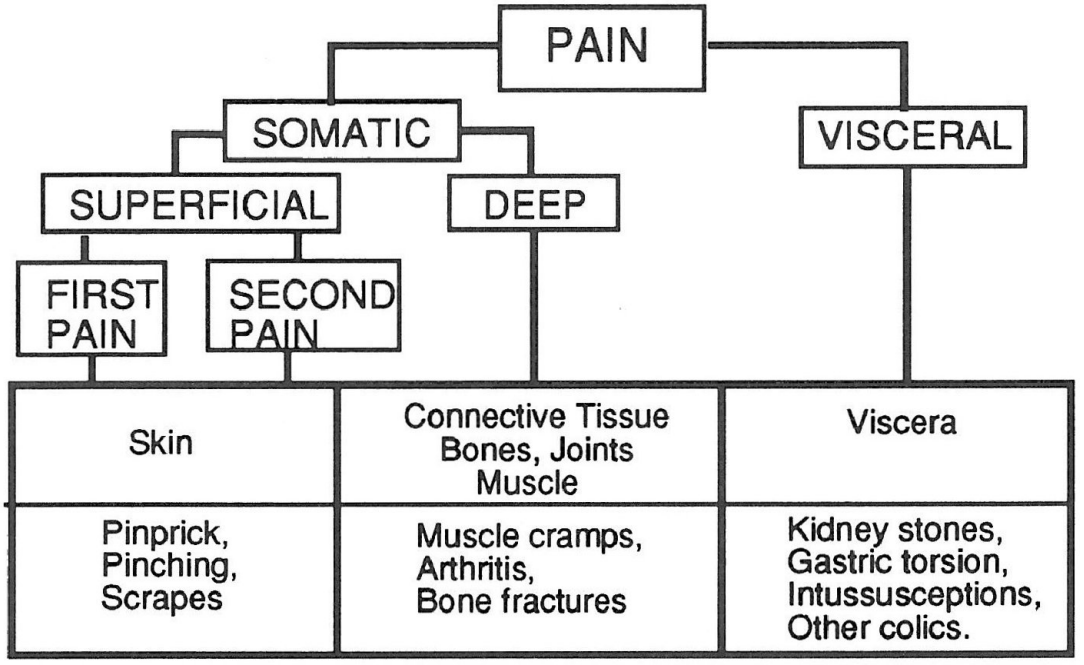

Figure 2. Types of pain (pain qualities). Sites and kinds of stimuli giving rise to each type of pain are shown in the lower boxes.

(5–35 m/s) and so are often called A delta nociceptors. *Polymodal nociceptors* respond to noxious mechanical stimuli, noxious or near noxious heat (> 40° C), and chemical irritants. They are mostly slowly conducting unmyelinated C fibers (0.5–1.5 m/s) with small receptive fields. C polymodal nociceptors are the predominant type in non-hairy skin. *Mechanothermal nociceptors* are activated by noxious mechanical or thermal stimuli. They are A delta fibers and probably function in reflex responses to noxious heat as impulses in C fibers conduct too slowly. These three populations of nociceptors have been found in both humans and animals.

The mechanism of activation of nociceptors is unclear. The rapidity of response to a stimulus of some primary afferents argues for some type of direct mechanical transduction mechanism. While pain receptors are most often described as free or bare, mechanonociceptors have a specialized keratinocyte/Schwann cell covering over their axonal endings in the epidermis which may contribute to their lack of response to innocuous stimuli. The sensitivity of polymodal nociceptors to several types of stimuli suggests some sort of chemical intermediate for activation. Several chemical agents (H^+, K^+, histamine, bradykinin, prostaglandins) are released from damaged tissue. These chemicals may mediate neuronal responses to noxious stimuli as well as the local vascular response. In addition, some chemicals can sensitize nociceptors to respond to innocuous stimuli. This sensitization may result in important adaptive behavioral responses to aid healing.

The sensory fiber which conveys nociceptive nerve impulses from the periphery to the spinal cord or the brain stem is referred to as a nociceptive primary afferent fiber. Except for the head, nociceptive primary afferents relay their impulse to the dorsal grey matter of the spinal cord via the dorsal roots. After they enter, their fibers split and may ascend or descend in the tract of Lissauer for several segments before synapsing in the dorsal horn. The dorsal horn has been subdivided into 10 layers or lamina based on cell types

and connections (*Rexed* 1952). The synaptic terminals of nociceptors are predominantly located in the superficial layers (Lamina I and the outer part of II). A significant number of A delta nociceptors also go to Lamina V. Both Lamina I and V contain cell bodies of neurons which project to the brain stem and thalamus. In the superficial layers A delta fibers make mostly axo-dendritic synapses. Their terminals may also be postsynaptic to other axons or dendrites. These latter two synapses are likely to be involved in modulation of ascending input by peripheral and central mechanisms.

There is much evidence that Substance P is the neurotransmitter released from nociceptive primary afferents. Substance P is excitatory to nociceptive spinal neurons and depletion of Substance P can cause hypalgesia. However, conclusive evidence that Substance P is specific to nociceptive afferents is lacking. Many other potential transmitters involved in nociception (somatostatin, vasoactive inhibitory peptide, cholecystokinin, glutamate, aspartate, bombesin) are found in primary afferents and in some cases are colocalized with substance P. As yet no distinct correlation of sensory receptor types with specific transmitters is apparent.

Although the preceding discussion refers to the mechanisms of transmission to the spinal cord, it is also applicable to sensory pathways of the head. Cranial nerves contain similar nociceptor afferents, and the trigeminal nucleus caudalis is analogous and continuous with the spinal cord dorsal horn.

Nociceptive ascending pathways

The majority of the cell bodies (called relay cells) giving rise to fibers which form nociceptive ascending pathways are found in the dorsal horn of the spinal cord where they form columns (sheets) of cells called lamina. Two classes of relay neurons are found in the dorsal horn which are involved in nociception. One set responds only to stimuli which are noxious. These cells are referred to as "nociceptive specific" (NS) neurons. The second set, called "wide dynamic range" (WDR) neurons (nonspecific nociceptive or multireceptive neurons) respond slightly to innocuous (light) mechanical stimuli but give a much stronger response when a noxious stimulus is applied in the periphery. The nociceptive specific neurons are found in both the superficial layer (marginal layer or lamina I) and the deeper layers of the dorsal horn. They usually have discrete receptive fields in the periphery, one to several square centimeters in size in the monkey. The cells are of two functional types, those which respond to noxious mechanical stimuli and the second group which respond to both noxious mechanical and to noxious heat stimuli. The wide dynamic range cells are seldom found in lamina I, but are mostly located in the deeper layers of the dorsal horn (lamina IV-VI) and in the lamina VII and VIII of the ventral horn in the lumbosacral enlargement of the spinal cord. The receptive fields of these neurons vary considerably in size. In some instances they may be confined to a single digit, in others, to a major portion of the leg. The receptive fields usually have a central zone where both innocuous and noxious stimuli excite the cell and a peripheral zone where only noxious stimuli can excite the cell. These cells respond to a variety of energies. Some respond to mechanical stimuli at the innocuous level, but not to warm stimuli, yet respond only to noxious heat, not to noxious mechanical stimulation. In the peripheral zone of the receptive fields, these cells act like specific heat nociceptors.

Nociceptive information is transmitted from the spinal cord to the brain by multiple ascending systems. The systems include a "lateral" group, consisting of 1) the neospinothalamic tract which ascends directly from the spinal cord to the thalamus; 2) the spinocervical tract which relays to the thalamus through the lateral cervical nucleus; and 3) the dorsal column-postsynaptic tract which relays to the thalamus through the dorsal column nuclei. The "medial" group

consists of 1) the paleospinothalamic tract which projects to the midline-intralaminar thalamic regions; 2) the spinoreticular tract which sends fibers throughout the reticular formation; 3) the spinomesencephalic tract which ends in the mesencephalon and 4) the propriospinal system which ascends the spinal cord using a diffuse, polysynaptic network of fibers and terminates in the reticular formation.

In humans and sub-human primates, the principal ascending nociceptive pathway in all species appears to be the neospinothalamic pathway, which is a spinal cord pathway which ascends the spinal cord on the opposite side of the body from that where the nociceptors and primary afferent fibers are located. The neospinothalamic pathway consists of both specific and wide dynamic range neurons. Located medial (deep) to the neospinothalamic pathway is the much smaller paleospinothalamic pathway. This pathway consists primarily of wide dynamic range cells. The spinoreticular pathways are located dorsal to and deep to the spinothalamic pathways. The spinoreticular pathway also is largely made up of wide dynamic range type cells. Anatomical evidence supports the presence of a spinomesencephalic, a dorsal column-postsynaptic pathway and a multiple neuronal pathway called the propriospinal pathway in humans as well as in animals.

In most non-primate animals, the nociceptive pathways are much more numerous, more diffuse and often ascend the spinal cord bilaterally. This has been definitively shown in the cat where, in the cervical region, the neospinothalamic pathway has a bilateral origin (*Carstens & Trevino* 1978). In the cat and swine, perception of pain arising from noxious stimulation of either side of the body is not lost by severing one side of the spinal cord as it is in primates (Cat: *Kennard* 1954; Swine: *Breazile & Kitchell* 1968). This may be due to the relatively larger propriospinal pathway in those species.

The sub-primates have a large spinocervicothalamic pathway which ascends the spinal cord ipsilaterally and crosses to the opposite side in, or cranial to, the first cervical segment. This pathway is largely transmitting low threshold mechanoreceptive (hair follicle receptor) activity, however it has been shown to consist of some cells that respond to noxious stimulation. The dorsal column-postsynaptic pathway has been extensively investigated in the rat, cat and the monkey. This pathway consists largely of cells which respond to low threshold mechanical stimulation although a number of wide dynamic range and a few nociceptive specific cells have been found.

Supraspinal structures involved in nociception

There are four major regions of the brain involved in nociception: 1) the medulla oblongata; 2) the mesencephalon; 3) the diencephalon; and 4) the cerebral cortex. The reticular formation constitutes part of the first three regions. It can be considered acting as a whole, as well as presented as part of the three major divisions of the brain. Functionally the reticular formation can be considered, as far as nociception is concerned, as consisting of three important subdivisions: 1) the ascending reticular activating system (ARAS), a network of long fibers which inter-relate with each other to project rostrally widely into the cerebral cortex to control the excitability of the cerebral cortex and play a major role in consciousness; 2) a series of descending systems which project down the spinal cord to modulate (or suppress) the relaying of nociceptive information to the brain; and 3) specific nuclei which send projection fibers to other parts of the brain which have rather specific effects upon nociceptive behaviour.

The medulla oblongata has cells in its medial part which contribute to the ARAS by projecting to the cerebral cortex through the medial and intralaminar thalamic nuclei. The medullary reticular formation contains

a number of nuclei which have been implicated in descending inhibition of nociception.

The mesencephalic reticular formation and the central (periaqueductal) gray receive nociceptive inputs from the medullary part of the reticular formation and the spinomesenphalic tracts. The spinal input to the periaqueductal gray appears to be, in part, through collaterals from spinothalamic tract fibers destined for the ventral posterolateral nucleus (VPL) of the thalamus. The cells of the mesencephalon have large receptive fields that may be bilateral. These cells contribute to the ARAS. Anatomical and electrophysiological studies indicate that the cells of the central gray project rostrally to synapse in midline and intralaminar nuclei of the thalamus; as well as caudally to the nuclei of the medulla. Electrical stimulation of the mesencephalic central gray produces a profound analgesia called stimulus produced analgesia or SPA.

The thalamus and the hypothalamus parts of the diencephalon are involved in nociception. The thalamus serves as the relay for most of the activity entering the cerebral cortex from the various sensory systems of the body, other than olfaction. The thalamus consists of a large number of highly complex nuclei. The thalamic nuclei associated with nociception can be divided into a ventral group (the ventral lateral nucleus [VL] and the ventrobasal nuclei, which consist of the ventral posterolateral nucleus [VPL] and the ventral posteromedial nucleus [VPM]); a medial posterior thalamic complex (PO_m); an intralaminar group (especially the parafascicular and the central lateral [CL] nuclei); a midline nuclear group; and a submedius nucleus. *Dennis & Melzack* (1977) emphasize that the lateral ascending spinal cord nociceptive pathways, which are associated with the sensory-discriminative dimension of pain, terminate predominately in the more laterally located nuclei of the thalamus (VPL, VPM, VL, and the PO_m). The medical ascending pathways terminate in more medial structures such as the intralaminar and midline nuclei of the reticular formation. The VPL relays information from the body, other than the head, to the cerebral cortical areas SI and SII, and the VPM relays information from the head to these same areas. These are the areas where specific mechanoreceptor system terminates. Selective lesions in the VPL, the VPM, or in the SI area will result in the loss of the ability to perceive mechanical stimuli applied to the specific regions in the periphery. Cells responding to the application of nociceptive stimuli have been recorded from in the VPL of all species studied. The cells were few in number compared to the number of low threshold mechanical cells found. Both nociceptive specific and wide dynamic range cells have been found. Most of the receptive fields were small and located on the contralateral side of the body. The receptive fields bore a somatotopic relationship to the location of the cells in the VPL. Major differences were found between the location of the cells in the monkey and the rat as compared to the cat. The majority of the cells in the cat were found in the "shell" region of the VPL (*Honda et al.* 1983, *Kniffi & Mizumura* 1983) similar in location to the terminations of the neospinothalamic tract (*Boivie* 1971, *Jones & Burton* 1974, *Berkley* 1980).

Other nociceptive nuclei in the thalamus are the medial part of the PO_m, the CL and the nucleus submedius. The cells of these nuclei, in general, respond to the application of strong noxious stimuli to large, bilateral receptive fields. These findings are consistent with the fact that only the nociceptive tracts belonging to the medial system (affectional-motivational dimension of pain) terminate in these nuclei.

The Cerebral Cortex: Historically, it has been only recently that the cerebral cortex has been definitely implicated as playing a major role in pain perception. Early neurologists proposed that pain, thermal sense and gross touch were sensed in the thalamus

rather than the cerebral cortex. Recent work demonstrates that pain has multiple representation in the cerebral cortex rather than none. *Willis* (1985) cites several lines of evidence that the cerebral cortex has an important role in the processing of pain sensation: 1) stimulation of the exposed cerebral cortex in humans sometimes produces pain; 2) lesions of the postcentral gyrus (ia. SI) may reduce pain; 3) pain is sometimes experienced in epileptic auras; and 4) lesions of the cortex can produce a syndrome resembling "thalamic" pain.

The limbic system plays an important role in pain. The periaqueductal gray of the mesencephalon is a part of the midbrain area that projects to the medial thalamus and the hypothalamus, which, in turn, project to the limbic system. Many of these areas interact with the frontal cortex. Electrical stimulation of parts of the limbic system, such as the hippocampus and the amygdala, evokes escape or other attempts to stop the stimulation (*Delgado et al.* 1956). After ablation of the amygdala and the overlying cerebral cortex, cats show marked changes in affective behaviour, including decreased responses to nociceptive stimulation (*Folz & White* 1962). Lesioning of the cingulate gyrus will drastically alter the motivational aspects of pain in the cronically ill human patient (*Corkin et al.* 1979). The evidence indicates that limbic structures, although they have a role in many other functions, provide a neural basis for the aversive drive and affect that comprise the motivational dimensions of pain (*Melzack* 1986).

Factors which modulate pain

Nociception is subject to a high degree of modulation in both animals and humans. These modulating factors include lesions of the central nervous system, the action of drugs, effects of focal brain stimulation, as well as more natural factors such as anxiety, attention, prior experiences, the co-occurrence of other noxious and non-noxious stimuli. Of special interest are intrinsic analgesic systems which are common to both animals and humans.

In addition to the complex system of ascending pathways necessary for pain perception, there are both local segmental systems and descending supra-spinal systems which inhibit pain signals. The segmental control depends on the relative amount of large fiber (innocuous) afferent activity vs small fiber (noxious) afferent activity. Large fiber activity inhibits the relay, or transmission cells, called "T" cells via presynaptic mechanisms in the substantia gelatinosa (SG). Small fiber activity excites the T cells directly and reduces the inhibition from the SG. Regardless whether presynaptic or postsynaptic inhibition is involved, opiates seem critical and GABA has been implicated in presynaptic mechanisms. Such segmental control of pain transmission may underlie the effectiveness of transcutaneous electrical nerve stimulation and acupuncture analgesia in both animals and humans.

The anatomical pathway for descending supraspinal inhibition involves fibers in the spinal cord dorsolateral funiculus (DLF). These fibers originate in the ventral portion of the rostral medulla. These medullo-spinal neurons function as the final common pathway for more rostral structures involved in descending inhibition.

Identifying the neurotransmitters involved in descending inhibition has been a confusing process and is far from complete. Multiple sites of action of a single transmitter, inconsistent effects at a given site, lack of selective antagonists, and co-localization of transmitters in single neurons have confounded attempts to elucidate specific actions of various transmitters. Different structures are likely to use different pharmacological agents. Norepinephrine, Substance P, acetylcholine, neurotensin, as well as others have been implicated in analgesic mechanisms but their functional importance and synaptic relationships are not yet clear. Nevertheless there is good evidence that serotonin (5-HT) and some endogenous opi-

ates (enkephalins and dynorphan) play important roles.

Serotonin is found in high concentrations in the nucleus raphe magnus in the rostral medulla, and its release at Lamina I and II in the spinal cord inhibits nociceptive cells. This inhibition may be direct postsynaptic inhibition or indirect via the excitation of an inhibitory opiate containing neuron. In addition 5-HT may be released at medullary sites where it can exite medullo-spinal cells.

The endogenous opiates are clearly involved in some but not all pain control systems. Opiate receptors are found at midbrain, medullary, and spinal sites. Injection of morphine at any one of these levels can cause analgesia; spinal application of opiates is now a common practice in humans. In animals, descending inhibition from some brain sites can be blocked by the opiate antagonist naloxone.

Ascending nociceptive tracts send collaterals to the periaqueductal gray and rostral ventromedial medulla. Such interactions between ascending nociceptive systems and areas known to be involved in descending inhibitory systems may explain the phenomena known as diffuse noxious inhibitory controls (DNIC). DNIC refers to the ability of noxious input from one body area to inhibit spinal neuronal responses to a coincident noxious input from a second body area (*Le Bars et al.* 1979). DNIC is dependent on a supra-spinal loop and has recently been shown to work on humans' perceptions of pain intensity (*Talbot et al.* 1987).

Intrinsic pain modulation systems may also be activated in animals by a variety of environmental stimuli, many of which are non-noxious (e.g. restraint, cold water swims, hypoglycemia, hypertension, footshock). This phenomena has been labeled stress induced analgesia or environmentally induced analgesia (EIA) (*Watkins & Mayer* 1986). That there are multiple pharmacologically distinct pain modulation systems at work is illustrated by the fact that EIA may be opiate mediated or not depending on the particular type of stimulus used. Another important factor seems to be the controllability of the stimulus. Animals given identical amounts of footshock only become analgesic via opiate mechanisms if they learn that they have no control over the stimuli (*Maier et al.* 1982). This certainly implicates the importance of higher brain centers in the processing of pain information in animals. Anecdotal reports of humans becoming analgesic in battle (*Beecher* 1959) or sporting events are suggestive of mechanisms similar to EIA at work.

Summary and conclusions

Pain is a perception depending upon the cerebral cortex being in a desynchronized state before it can occur. In order for a noxious stimulus to lead to the perception of pain, the stimulus must be of sufficient intensity to cross the pain detection threshold. Evidence is available which indicates that an animal can detect pain at the same stimulus intensity level that humans detect pain. In animals, the intensity of the pain above the pain detection level is very difficult to assess from observations of the behaviour of the animal, particularly the animal's reflex responses to the stimulus. Animals show considerable variation in their tolerance to a particular stimulus depending upon the species, the breed, their previous experience with similar stimuli, their anxiety state, their environment, and many other factors. In the assessment of pain in animals, the intensity of a particular stimulus should be correlated with an adult human's assessment of a similar stimulus, not unlike what one would do in assessing a child's response to a noxious stimulus. Stoic animals may give few indications that they are detecting a stimulus as pain, however, above the pain detection level, they may be suppressing not only their response to the pain, but also the amount of pain being felt through endogenous pain suppression mechanisms. The pain suppression capability varies considerably among humans because of inherent as well as lear-

ned suppression. Evidence is available that also animals have inherent as well as learned pain suppression.

References

Beecher HK: Measurement of Subjective Responses, New York, Oxford Univ. Press, 1959.

Berkley KJ: Spatial relationships between the terminations of somatic sensory and motor pathways in the rostral brainstem of cats and monkeys. J. Comp. Neurol. 1980, *193,* 283–317.

Boivie J.: The termination of the spinothalamic tract in the cat. An experimental study with silver impregnation methods. Exp. Brain Res. 1971, *12,* 331–353.

Breazile JE, Kitchell RL: Ventrolateral spinal cord afferents to the brain stem in the domestic pig. J. Comp. Neurol. 1968, *133,* 363–373.

Carstens E, Trevino DL: Anatomical and physiological properties of ipsilaterally projecting spinothalamic neurons in the second cervical segment of the cat's spinal cord. J. Comp. Neurol. 1978, *182,* 167–184.

Corkin S, Twitchell TE, Sullivan EV: Safety and efficacy of cingulotomy for pain and psychiatric disorders. In: Modern Concepts in Psychiatric Surgery, eds. Hitchcock ER, Ballentine Jr HT, Myerson BA, New York, Elsevier, 1979, 253.

Delgado JMR, Rosvold HE, Looney E: Evoking conditioned fear by electrical stimulation of subcortical structures in the monkey brain. J. Comp. Physiol. Psychol. 1956, *49,* 373–380.

Dennis SG, Melzack R: Pain-signalling systems in the dorsal and ventral spinal cord. Pain 1977, *4,* 97–132.

Folz EL, White LE: Pain "relief" by frontal cingulumotomy. J. Neurosurg. 1962, *19,* 89–100.

Honda CN, Mense S, Perl ER: Neurons in ventrobasal region of the cat thalamus selectively responsive to noxious mechanical stimulation. J. Neurophysiol. 1983, *49,* 662–673.

Jones EG, Burton H: Cytoarchitecture and somatic sensory connectivity of thalamic nuclei other than the ventrobasal complex in the cat. J. Comp. Neurol. 1974, *154,* 395–432.

Kennard MA: The course of ascending fibers in the spinal cord of the cat essential to the recognition of painful stimuli. J. Comp. Neurol. 1954, *99,* 511–524.

Kitchell RL: Problems in defining pain and peripheral mechanisms of pain. J.A.V.M.A. 1987, *191,* 1195–1199.

Kitchell RL, Guinan MJ: The nature of pain in animals. In: The Experimental Animal in Research, Vol. I, eds. Rollin BE, Kesel ML, Boca Raton, CRC Press, 1990, pp. 185–203.

Kitchell RL, Johnson RD: Assessment of pain in animals. In: Animal Stress, ed. Moberg GP, Bethesda, Amer. Physiol. Soc., 1985, pp. 113–140.

Kniffi KD, Mizumura K: Responses of neurons in the VPL and VL-VPL region of the cat to algesic stimulation of muscle and tendon. J. Neurophysiol. 1983, *49,* 649–661.

Le Bars D, Dickenson AH, Besson JM: Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurons in the rat. Pain 1979, *6,* 283–304.

Maier SF, Drugan RC, Grau JW: Controllability, coping behaviour, and stress induced analgesia in the rat. Pain 1982, *12,* 47–56.

Melzack R: Neurophysiological foundations of pain. In: The Psychology of Pain, ed. Sternbach RA, New York, Raven Press, 1986, pp. 1–24.

Rexed B: The cytoarchitectonic organization of the spinal cord in the cat. J. Comp. Neurol. 1952, *96,* 415–496.

Sherrington CS: The Integrative Action of the Nervous System. New York, Scribner, 1906.

Talbot JD, Duncan GH, Bushnell MC, et al.: Diffuse noxious inhibitory controls (DNIC): Psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. Pain 1987, *30,* 221–232.

Vierck Jr CJ: Extrapolations from the pain research literature to problems of adequate veterinary care. J.A.V.M.A. 1976, *168,* 510–517.

Watkins LR, Mayer DJ: Multiple endogenous opiate and non-opiate analgesia systems: evidence for their existence and clinical implications. In: Annals of the New York Academy of Sciences, 1st International Conference on Stress Induced Analgesia, Vol. 467, ed. Kelly DD, New York: NYAS Press, 1986, pp. 273–299.

Willis Jr WD: Nociceptive transmission to the thalamus and the cerebral cortex. In: The Pain System. The Neural Basis of Nociceptive Transmission in the Mammalian Nervous System, ed. Willis Jr WD, Basel, Karger, 1985, pp. 211–263.

Zimmermann M: Neurobiological concepts of pain, its assessment and therapy. In: Neurophysiological Correlates of Pain, ed. Bromm B, Amsterdam, Elsevier, 1984, pp. 15–35.