Organization of Endogenous Opiate and Nonopiate Pain Control Systems

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Summary. Research during the past decade has revealed the existence of neural systems that modulate pain transmission. Much of this work has focused on the role of endogenous opiate systems, but recent research indicates the involvement of nonopiate mechanisms as well. In this article, we present data demonstrating that opiate and nonopiate analgesia systems can be selectively activated by different environmental manipulations and describe the neural circuitry involved. Both neural and hormonal pathways and both opiate and nonopiate substances play roles in the complex modulation of pain transmission. The existence and description of these modulatory mechanisms have important clinical implications for the treatment of pain.

A major advance in our conception of the neural processing of pain has occurred in the past decade. It has become clear that information about tissue damage is not passively received by the nervous system, but is filtered, even at the first sensory synapse, by complex modulatory systems (*1*). The discovery of these systems has fostered, and in turn been fostered by, the notion that the central nervous system contains endogenous substances, endorphins, having analgesic properties virtually identical to opiates of plant and synthetic origin. In this article, we examine the development of these concepts and present new evidence unequivocally demonstrating environmentally activated, endorphin-mediated, pain-modulating mechanisms in the central nervous system. In addition, we provide evidence that certain environmental stimuli activate other, nonopiate, pain-modulatory systems as well. Finally, the existence of multiple pain-modulatory systems is used to clarify the bewildering profile of clinical observations resulting from various pain treatments.

Historical Perspective

It has long been recognized that no simple invariant relationship exists between stimulus intensity and the magnitude of pain perception. Earlier models of pain perception recognized this phenomenon despite the lack of direct evidence to support it (*2*). The first impetus for the detailed study of circuitry to modulate pain resulted from the observation that electrical stimulation of the brain could suppress the perception of pain (*3*). Further investigation of stimulation-produced analgesia (SPA) provided considerable detail about the neural circuitry involved. Several similarities between these observations and information emerging from a concomitant resurgence of interest in the mechanisms of opiate analgesia (OA) were recognized.

These studies revealed that (i) effective loci for both OA and SPA lie within the periaqueductal and periventricular gray matter of the brainstem (*4*); (ii) OA and SPA are both mediated by the activation of a centrifugal control system, the output of which descends via the dorsolateral funiculus of the spinal cord (*5*); and (iii) the ultimate inhibition of the transmission of nociceptive information occurs at the initial processing stages in the spinal cord dorsal horn and homologous trigeminal nucleus caudalis by selective inhibition of nociceptive neurons (*6*).

In addition to these correlative observations, studies of SPA produced direct evidence of mechanisms in the central nervous system that depend on endogenous opiates (*1*). (i) Subanalgesic doses of morphine synergized with subanalgesic brain stimulation to produce behavioral analgesia (*7*); (ii) tolerance, a phenomenon invariantly associated with repeated administration of opiates, developed to the analgesic effects of brain stimulation (*8*); (iii) cross-tolerance developed between the analgesic effects of brain stimulation and opiates (*8*); and (iv) SPA was at least partially antagonized by naloxone, a specific narcotic antagonist (*9*). This last observation, in particular, could be most parsimoniously explained if electrical stimulation resulted in the release of an endogenous opiate-like factor (*10*). Indeed, naloxone antagonism of SPA was a critical impetus leading to the eventual discovery of such a factor (*11*).

Coincidental with work on SPA, another discovery of critical importance for our current concepts of endogenous analgesia systems was made. Several laboratories almost simultaneously reported the existence of stereospecific binding sites for opiates in the central nervous system (*12*). These "receptor" sites were subsequently shown to be localized to neuronal synaptic regions (*13*) and to overlap anatomically with loci active in the neural processing of pain (*14*). That an opiate receptor exists suggested that an endogenous compound with opiate properties also exists. In 1974, Hughes and Kosterlitz (*15*) reported that they had isolated a factor (enkephalin) with such properties from neural tissue. Subsequent work has characterized this and other neural and extraneural compounds with opiate properties (*16*). As with the opiate receptor, the anatomical distribution of endogenous opiate ligands overlaps with sites involved in pain processing (*17*).

Thus, the existence of an endogenous OA system is suggested by several lines of evidence. Electrical stimulation of the brain produces analgesia. The anatomical structures and neural mechanisms involved in SPA parallel those of OA, and strong evidence exists that an endogenous opiate is involved in SPA. The central nervous system contains opiate binding sites and endogenous ligands capable of interacting with those sites.

Analgesia Produced by Environmental Stimuli

The demonstration of a well-defined neural system capable of potently blocking pain transmission suggests, but by no means proves, that the function of this system is to modulate the perceived intensity of noxious stimuli. If this system has such a physiological role, the amount

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of activity within the system might be influenced by environmental stimuli. Identifying environmental situations that produce analgesia would give credence to the idea that invasive procedures, such as brain stimulation or narcotic drugs, inhibit pain by mimicking natural activity within these pathways. In addition to providing a more complete understanding of the centrifugal control of pain, such information might suggest ways of relieving pain by less invasive means.

A systematic search for environmental stimuli that activate pain-inhibitory systems was begun by Hayes *et al.* (*18*). They discovered that potent analgesia could be produced by such diverse stimuli as brief footshock, centrifugal rotation, and injection of intraperitoneal hypertonic saline. These effects seemed specific to pain perception insofar as normal motor behavior, righting and corneal reflexes, vocalization, startle responses, and response to touch remained unimpaired (*18*). Two additional concepts emerged. First was the conclusion that exposure to stress was not sufficient to produce analgesia. Although all environmental stimuli producing analgesia are stressors (*19*), the failure of classical stressors, such as ether vapors and horizontal oscillation, to inhibit pain indicated that stress was not the critical variable (*18*). Second was the unexpected finding that the opiate antagonist naloxone did not block environmentally induced analgesias (*18*). Therefore, it appeared that nonopiate systems must exist in addition to the opiate system described earlier.

Although the stimuli studied by Hayes *et al.* (*18*) did not seem to activate an opiate system, subsequent investigations found clues that brain endorphins might act in at least some types of environmentally induced analgesias. Akil and coworkers (*20*) studied the analgesic effects of prolonged footshock. They found, in contrast to the results of Hayes *et al.* (*18*), that naloxone did partially antagonize the analgesia. This initial indication of opiate involvement led Akil and her colleagues to look for biochemical evidence that footshock released brain opiates. They found that changes in brain opiate levels paralleled the development of footshock-induced analgesia (FSIA) (*20*). When rats became tolerant to the analgesic effects of footshock, brain opiate concentrations returned to control values (*20*). In agreement with these results, tritiated Leu-enkephalin binding has been reported to decrease as analgesia increases (*21*). Although these data show that opiates are released by footshock, biochemical studies can provide evidence only for a correlative, not a causal, relationship between opiate release and analgesia.

The controversy over the involvement of opiates in FSIA was resolved in part by Lewis *et al.* (*22*), who wondered whether the difference in duration of footshock used by Hayes *et al.* (*18*) and Akil *et al.* (*20*) might explain the difference in their results. By comparing the effects of naloxone on analgesia produced by brief (3 minutes) and prolonged (30 minutes) footshock, Lewis *et al.* (*22*) showed that only the latter could be blocked by naloxone. This suggested that different analgesia systems become active as the duration of footshock increases.

Concurrently we observed during the course of other experiments that brief shock restricted to the front paws produced an analgesia that could be reversed by naloxone, as measured by the tail-flick assay (*23*). We were puzzled by this analgesia since Hayes *et al.* (*18*) and Lewis *et al.* (*22*) found that brief shock produced nonopiate analgesia. This led us to use a blind procedure (*24*) to test whether naloxone had different effects on analgesia produced by shock to the front paws as opposed to the hind paws (*25*). We found that the effects of naloxone differed depending on the body region shocked. Front paw shock seems to activate an opiate system, since low doses of naloxone antagonized this analgesia (Fig. 1A). In contrast, even high doses of naloxone failed to reduce analgesia induced by hind paw shock (Fig. 1D); a nonopiate system thus seems to be involved in this response.

Definitive conclusions about opiate involvement in neural systems are tenuous when based exclusively on the effects of narcotic antagonists, which have effects on nonopiate systems as well (*26, 27*). Thus additional lines of evidence are required to infer that opiates mediate front paw FSIA. If opiates are involved, front paw FSIA should also be reduced in rats made tolerant to opiates. To test for such cross-tolerance between mor-

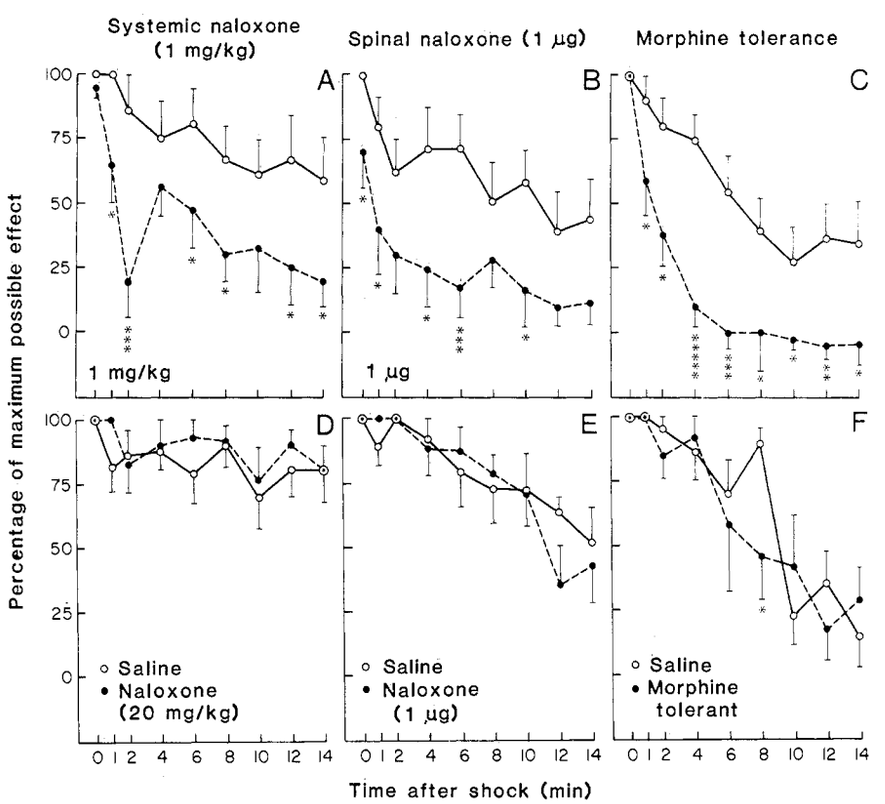


Fig. 1. Evidence for opiate analgesia produced by brief front paw shock (A to C) and nonopiate analgesia produced by brief hind paw shock (D to F). Endogenous opiates seem to mediate front paw FSIA since it is significantly attenuated by systemic naloxone (A), 1 μg of spinal naloxone (B), and morphine tolerance (C). Antagonism of front paw FSIA by systemic naloxone seems to be a specific effect since naloxone doses as low as 0.1 mg per kilogram of body weight significantly attenuate the analgesic state. In contrast, nonopiate systems mediate hind paw FSIA since it fails to be significantly attenuated either by high doses (20 mg/kg) of systemic naloxone (D), 1 μg of spinal naloxone (E), or morphine tolerance (F). $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .005$, $^{*****}P < .0005$; one-tailed *t*-tests.

phine analgesia and front paw FSIA, we continuously infused rats with either morphine or saline for 6 days (*25, 28*). At this time, the rats infused with morphine were tolerant to this opiate since 10 milligrams of morphine per kilogram of body weight no longer produced analgesia. When the rats were tested for front paw FSIA, analgesia was greatly reduced in morphine-tolerant rats (Fig. 1C). Since front paw FSIA shows cross-tolerance with morphine and is antagonized by naloxone, the involvement of an endogenous opiate system in this type of analgesia stands on firm ground.

By the same procedure, we tested rats for cross-tolerance between morphine analgesia and hind paw FSIA (*25*). No cross-tolerance was observed (Fig. 1F). The absence of an effect of high doses of naloxone (Fig. 1D) or morphine tolerance (Fig. 1F) on hind paw FSIA demonstrates that this manipulation activates an independent nonopiate analgesia system. Since identical shock parameters were used in the hind paw and front paw experiments, these results show that factors other than exposure to stress determine whether nonopiate or opiate systems are activated.

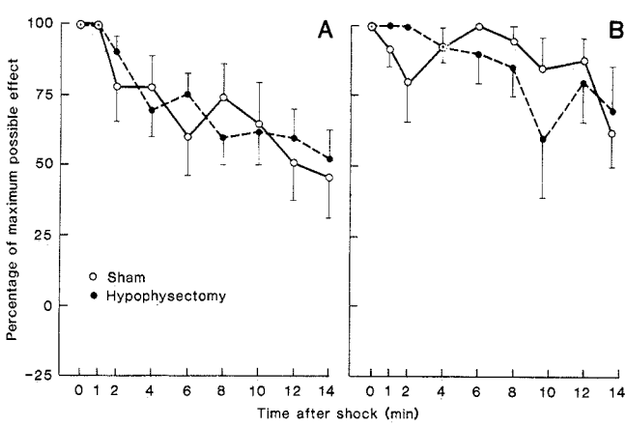
We have studied both front paw and hind paw FSIA to define how these opiate and nonopiate environmental analgesias are produced. We will first look at the opiate analgesia produced by front paw shock. Several similarities will be seen to exist between the opiate analgesias produced by front paw shock and morphine.

Opiate Analgesia Systems: New Data

The fact that endogenous opiates are involved in front paw FSIA does not prove that this effect is mediated by the same circuitry as morphine analgesia. A critical question was whether front paw FSIA could be accounted for by release of opiates from the pituitary or sympathetic-adrenal medullary axis, since footshock causes opiate release from these sites (*19*). Since hypophysectomy failed to reduce front paw FSIA (Fig. 2) (*29*), pituitary β-endorphin is not necessary for front paw FSIA. Since adrenalectomy and sympathetic blockade actually potentiated front paw FSIA (*29*), this analgesia is not produced by opiates from the sympathetic nervous system. These data strongly suggest that front paw FSIA, like morphine analgesia, operates through opiate pathways within the central nervous system.

On the basis of these results, we began to search for the neural pathways involved in front paw FSIA. Since the spinally mediated tail-flick reflex is inhibited by front paw footshock, the circuitry for the observed inhibition either exists entirely within the spinal cord or results from the activation of a centrifugal control system in the brain that then descends to the spinal cord. We therefore examined the effects of spinal cord lesions (*30*), and found that front paw FSIA is abolished by lesions of the dorsolateral funiculus (DLF) of the spinal cord (Fig. 3). High cervical (C3) DLF lesions leave all potential pathways intact between the front paws, which receive the stimulus, and the tail, which is tested for pain sensitivity (Fig. 4). Since high cervical DLF lesions abolish front paw FSIA, analgesia is not produced through direct intraspinal pathways. Therefore, front paw shock, like morphine (*5*), activates areas within the brain that inhibit pain via descending pathways within the DLF. Furthermore, we have shown with brain lesion studies that, for front paw FSIA as well as morphine analgesia, this descending DLF pathway arises from the nucleus raphe alatus (*31–33*). In addition, we have shown that all of the critical circuitry for this analgesic effect exists below the level of the mesencephalon, since midcollicular decerebration has no effect on the analgesia (*33*).

At this point, front paw FSIA has been characterized as a neural, opiate-mediated phenomenon; analgesia is produced by activating brain sites that inhibit pain by way of descending pathways within the DLF. Yet none of this information pinpoints the location of the opiate synapse. To determine the possible involvement of a spinal cord site of action, intrathecal catheters were implanted such that the tips ended at the lumbosacral enlargement. Naloxone could be delivered to the level of the spinal cord controlling the tail-flick reflex, the behavioral measure used to assess pain threshold. Immediately before front paw shock, rats were injected with either saline or 1 microgram of naloxone. Spinal naloxone significantly antagonized



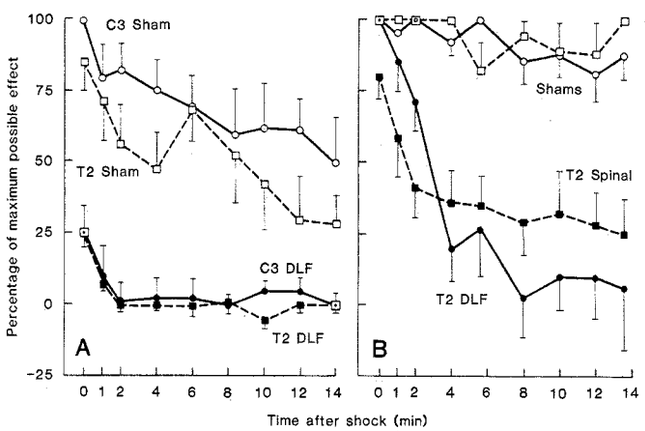


Fig. 2 (left). Effect of hypophysectomy on front paw (A) and hind paw FSIA (B). The failure of hypophysectomy to reduce FSIA in animals with lesions demonstrates that pituitary β-endorphin and other pituitary factors are not necessary for the production of analgesia. These data, plus the failure of adrenalectomy to reduce FSIA, suggest that these analgesic effects are mediated by neural rather than hormonal pathways. Fig. 3 (right). Effect of bilateral DLF lesions and spinal transection on front paw (A) and hind paw FSIA (B). (A) Bilateral DLF lesions at either the second thoracic (*T2*) or third cervical (*C3*) vertebral levels virtually abolish front paw FSIA. Since DLF lesions at C3 leave intact all potential intraspinal connections between the level of stimulus input (front paws) and the lumbosacral cord (controlling the tail-flick response), direct-intraspinal pathways cannot be involved in this analgesic response; pain inhibition must be mediated by supraspinal sites that inhibit pain via descending pathways within the DLF. (B) Bilateral DLF lesions at T2 attenuate, but do not abolish, hind paw FSIA. Immediately after shock termination (0 minute), profound analgesia was observed, which then slowly dissipated. No further significant reduction in analgesia was observed after T2 spinal transection. These results imply that descending pathways involved in hind paw FSIA exist only within the DLF and that intraspinal pathways account for the remaining analgesia.

front paw FSIA (Fig. 1B). This effect cannot be attributed to a spread of the drug to the brain since the same dose delivered to the high thoracic cord (farther from the level controlling the tail-flick reflex yet closer to the brain) failed to reduce front paw FSIA. These experiments demonstrate that an opiate synapse critical to the production of front paw FSIA exists within the spinal cord (*34*).

One intriguing aspect of this effect is that naloxone can prevent, but cannot reverse, front paw FSIA (Fig. 5). When this opiate antagonist was injected onto the spinal cord immediately after the brief (90 seconds) shock, analgesia was not reduced (*34*). Naloxone was effective only if delivered before analgesia was induced. This result implies that briefly activating the system causes activity within the spinal cord to perseverate independently of continued opiate release. These results lead us to speculate that these endogenous spinal opiates may act as neuromodulators of postsynaptic activity, rather than as classical neurotransmitters.

In summary, front paw shock produces a neural OA which depends on a pathway originating within the nucleus raphe alatus and descending through the DLF (Fig. 6). In turn, these descending DLF axons activate, either directly or indirectly, a critical opiate synapse within the cord. Once this spinal circuitry is activated by the endogenous opiate, the neural response may perseverate independent of further opiate release. As will be seen in the next section, the neural basis of hind paw and front paw FSIA are distinct.

Nonopiate Analgesia Systems: New Data

A parallel series of experiments examined the nonopiate analgesia produced by hind paw shock. We found that this effect is also neurally, rather than hormonally, mediated, since analgesia was not reduced by removal of the pituitary (Fig. 2) or the adrenal glands (*29*). This result led to studies aimed at identifying the neural substrates of hind paw FSIA. Spinal lesion studies (*30*) showed that this effect, like front paw FSIA, is mediated through descending pathways within the DLF (Fig. 3). However, since lesions of the nucleus raphe alatus failed to abolish hind paw FSIA, the neural substrate of this effect is distinct from that of front paw FSIA (*33*). A further difference between the analgesias produced by front paw and hind paw shock

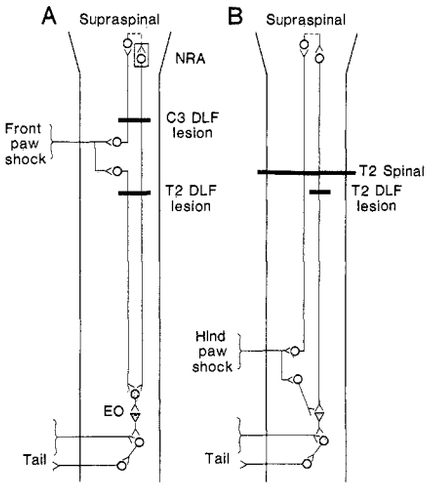


Fig. 4. The neural circuitry of front paw (A) and hind paw FSIA (B). (A) The demonstration that both T2 and C3 DLF lesions virtually abolish front paw FSIA implies that direct intraspinal pathways cannot be involved in this pain inhibition, since any potential neural pathway between the front paws (which receive the shock) and tail (which is tested for analgesia) remains intact after C3 lesions. Therefore, front paw shock activates supraspinal structures that mediate analgesia via a descending pathway lying within the DLF. Antagonism of front paw FSIA by intrathecal naloxone indicates that a critical opiate synapse exists within the spinal cord. (B) Hind paw FSIA is also mediated, in part, by an ascending-descending loop, since T2 DLF lesions significantly attenuate, but do not abolish, hind paw FSIA. Unlike front paw FSIA, hind paw FSIA is also mediated by intraspinal pathways, since significant and prolonged analgesia is observed after T2 spinal transection. Abbreviations: *EO*, endogenous opiate; *NRA*, nucleus raphe alatus.

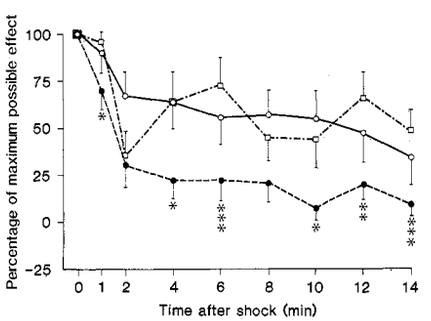


Fig. 5. The differential effect of naloxone delivered before and after the induction of front paw FSIA. Delivery of 1 μg of naloxone to the lumbosacral cord immediately before brief front paw shock significantly attenuates subsequent analgesia. In contrast, this same dose delivered less than 1 minute after front paw shock failed to attenuate the analgesia. The failure of naloxone delivered after shock to be effective at any time during the 14-minute test is in no way accounted for by the temporal delay of the naloxone injection since, at maximum, there was only a 4-minute difference in the time that these two groups received the drug. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .005$. One-tailed *t*-tests. Symbols: □, saline controls; ○, naloxone after shock; ●, naloxone before shock.

is that hind paw FSIA is only reduced, not abolished, by DLF lesions. Therefore, it seemed possible that the existence of a second descending pathway could account for the potent analgesia remaining. However, a comparison of hind paw FSIA in animals with transected spinal cords or DLF lesions indicated that an intraspinal, rather than descending, pain-inhibitory system is responsible for the analgesia observed after DLF lesions, since transecting the spinal cord did not further reduce the pain-inhibitory effects of hind paw shock (Figs. 3 and 4). Thus, segmental circuitry and descending pathways within the DLF account for the entire analgesic response to hind paw shock (Fig. 6). As with front paw FSIA, the supraspinal component of hind paw FSIA is mediated below the level of the mesencephalon, since it is unaffected by decerebration (*33*).

Plasticity In Analgesia Systems: New Data

An intriguing aspect of FSIA is that plasticity exists in the neural circuitry. Using a Pavlovian classical conditioning paradigm, Hayes *et al.* (*18*) found that rats readily associated environmental cues with the delivery of shock, and learned to activate their endogenous pain-inhibitory systems when these cues were presented. In that study, the nonelectrified shock chamber was the conditioned stimulus (CS), grid shock delivered to all four paws was the unconditioned stimulus (UCS), and tail-flick inhibition was the unconditioned response (UCR). After CS-UCS pairings, exposure to the nonelectrified grid reliably induced analgesia.

Since we have now demonstrated that front paw FSIA is mediated through a well-defined centrifugal opiate pathway, we used brief front paw shock as the UCS in a classical conditioning procedure to determine whether plasticity exists in opiate systems (*30*). The following section summarizes the evidence that animals can learn to activate their endogenous opiate systems to inhibit pain.

Exposure to the nonelectrified grid (CS) produced potent analgesia after being paired with front paw shock (Fig. 7) (*35*). The observation that classically conditioned analgesia can be antagonized by systemic naloxone (Fig. 7), spinal naloxone, and morphine tolerance suggests that animals learn to activate an endogenous opiate system (*30*). Maintenance of the analgesic state again seems to be independent of continued opiate

release. As with front paw FSIA (Fig. 5), we have observed that naloxone can prevent, but cannot reverse, classically conditioned analgesia (*30*).

Although opiate (front paw) and nonopiate (hind paw) FSIA can be differentially elicited, classically conditioned analgesia seems always to involve opiate pathways regardless of the body region shocked during conditioning trials. Classically conditioned analgesia can be antagonized by naloxone regardless of whether front paw or hind paw shock is used as the UCS (Fig. 7) (*30*).

The OA produced by these classical conditioning procedures seems to be neurally, rather than hormonally, mediated, since it is not attenuated by either hypophysectomy or adrenalectomy (*29*). Furthermore, classical conditioning involves supraspinal circuitry, since our studies have shown that conditioned analgesia is abolished by bilateral DLF lesions (*30*). As with front paw FSIA, lesions of the nucleus raphe alatus abolish the effect. As might be expected with a higher order behavior, however, decerebration abolishes the effect as well (*33*). Finally, the role of the periaqueductal gray matter in the neural circuitry of endogenous analgesia systems is beginning to become clear, since lesions there reduce the conditioned effect, but not the acute effects of footshock (Fig. 6) (*33*).

Multiple Pain Inhibitory Systems

These studies of front paw FSIA, hind paw FSIA, and classically conditioned analgesia provide strong support for the existence of multiple endogenous pain-modulatory systems within the central nervous system. At least three systems have been identified (Figs. 4 and 6). The first two pathways, which mediate the neural nonopiate analgesia observed after hind paw shock, consist of an intraspinal pathway and a descending DLF pathway with supraspinal origin. The third is a neural OA produced by front paw shock or by classical conditioning with front paw or hind paw shock as the UCS. This OA acts solely via descending pathways within the DLF and depends on an opiate synapse within the spinal cord. Thus, front paw FSIA and classically conditioned analgesia provide the first unequivocal demonstrations of neural opiate pathways activated in response to environmental stimuli.

A review of the literature, however, indicates that even these three systems do not account for all of the pain inhibitory responses reported. Currently available evidence indicates that four classes of analgesia exist: neural-opiate, hormonal-opiate, neural-nonopiate, and hormonal-nonopiate (Table 1).

The neural-opiate class includes the analgesia produced by morphine, electrical brain stimulation, front paw shock, and classical conditioning. The analgesias induced by these manipulations are strikingly similar (Table 1); none is attenuated by removal of the pituitary or adrenal glands, and each is reduced or abolished by naloxone, morphine tolerance, and DLF lesions. Although controversy exists regarding the role of the nucleus raphe alatus in the analgesia produced by electrical brain stimulation and systemic morphine (*36*), recent studies in our laboratory have demonstrated that lesions of this area virtually abolish analgesia produced either by morphine microinjection into the periaqueductal gray matter or by front paw shock (*32, 33*). Thus, at least one neural opiate system seems to activate centrifugal pain inhibitory pathways originating within the nucleus raphe alatus and descending within the DLF of the spinal cord.

Analgesia produced by electrical brain stimulation is a special case in that it belongs to two classes—neural-opiate and neural-nonopiate. Although morphine analgesia and SPA are similar (*1*), brain stimulation seems to activate both opiate and nonopiate pain-inhibitory systems. Naloxone has a variable effect on SPA ranging from no effect to complete reversal (*37*). Part of this variability is accounted for by the site of stimulation. Prieto *et al.* (*38*) have reported that stimulation sites ventral to the dorsal raphe support an analgesia that naloxone can reverse, whereas SPA elicited from more dorsal areas cannot be reversed by this opiate antagonist. The fact that cross-tolerance between morphine analgesia and SPA is incomplete implies that a nonopiate component exists for SPA (*8*).

Nonopiate mechanisms are involved in other neural analgesia systems as well. Naloxone and morphine tolerance fail to attenuate the analgesia induced by brief shock of either the hind paws or all four paws (Table 1). Although the neural substrates of these analgesias have not been as well characterized, hind paw FSIA is known to be significantly attenuated by bilateral DLF lesions. Thus, for every analgesic manipulation studied to date, the DLF seems to be a final common pathway for neural pain-inhibitory systems.

Exclusively neural opiate and non-

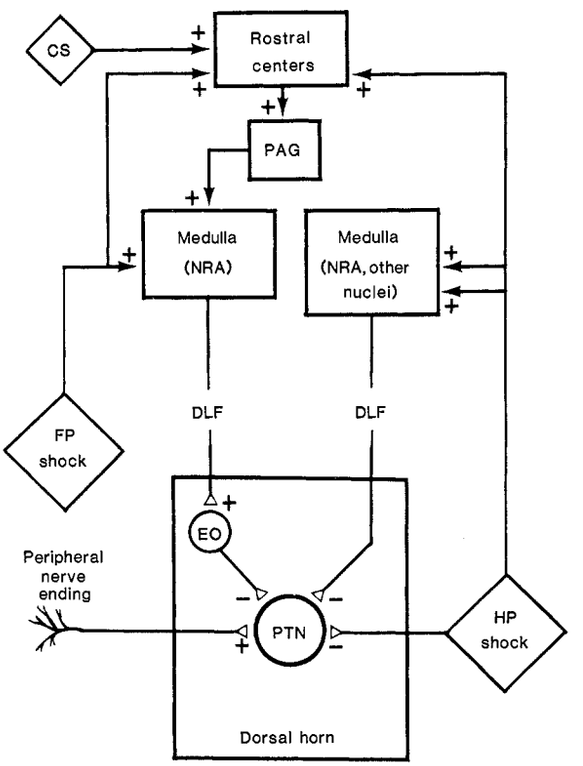


Fig. 6. Neural circuitry mediating front paw (*FP*) (opiate) FSIA, hind paw (*HP*) (nonopiate) FSIA, and classically conditioned (opiate) analgesia. Front paw shock activates the nucleus raphe alatus (*NRA*) within the ventral medulla. This nucleus sends a descending projection through the DLF to the dorsal horn of the spinal cord. In turn, endogenous opiates are released, inhibiting pain transmission neurons (*PTN*). Hind paw shock inhibits pain transmission neurons via two nonopiate pathways: an intraspinal pathway and a descending DLF pathway. The latter originates from the nucleus raphe alatus and from some other yet unidentified medullary area or areas. Classically conditioned (opiate) analgesia seems to result from activation of the same output pathway as front paw (opiate) FSIA. After conditioning trials in which the conditioned stimulus is paired with either front paw or hind paw shock (the unconditioned stimulus), the conditioned stimulus becomes capable of activating rostral centers in the brain, which, in turn, activate the periaqueductal gray (*PAG*) and subsequently the nucleus raphe alatus. This results, via a descending DLF pathway, in the release of endogenous opiates within the dorsal horn, producing analgesia.

opiate pathways cannot account for all of the types of analgesia that have been observed. Phenomena such as acupuncture analgesia, analgesia produced by prolonged shock of all four paws, and immobilization-induced analgesia are distinguishable from neural analgesias since removal of the pituitary or adrenal glands attenuates or abolishes their pain-inhibitory effects (*39*). These three types of analgesia constitute the hormonal-opiate class (Table 1) since each requires endogenous opiates, in addition to endocrine factors, to inhibit pain. Beyond this point, however, the underlying bases of these phenomena are far from understood. (i) The critical hormone or hormones involved in the production of analgesia have yet to be unequivocally identified for any of these manipulations. (ii) It is not known whether these humoral agents act directly at the level of the spinal cord to inhibit pain or whether they activate supraspinal sites which produce analgesia via descending neural pathways. Activation of descending pathways does seem to underlie at least one form of hormonal-opiate analgesia since DLF lesions partially block the analgesic effect of acupuncture in rabbits (*40*). If the mediation of acupuncture by descending DLF pathways proves to be indicative of this class, the distinction between hormonal-opiate and neural-opiate analgesia may simply be a difference in the mechanism by which supraspinal pain modulation systems are activated.

The endocrine system also seems to be involved in hormonal-nonopiate analgesia since members of this class depend on the integrity of the pituitary gland (Table 1) (*41*). Beyond this point, however, virtually nothing is known regarding the underlying bases of these analgesic effects.

Clinical Relevance of Endogenous Pain Inhibitory Systems

Much experimental evidence has accumulated regarding endogenous pain-modulation systems in animals. These systems may also modulate pain in humans. A number of distinct modulatory systems have been identified under controlled laboratory conditions. In the more naturalistic circumstances of clinical research, it is likely that more than one of these systems may be active at any given time, which may account for the variability and controversy in the clinical literature.

Endogenous pain-modulatory systems may be active in at least two situations in humans. The first involves the basal, tonic activity within these systems and allows the experimenter to assess whether pain inhibition occurs continuously, at least to some degree. The second in-

Table 1. Summary of available data on endogenous analgesia systems (*1*, *20*, *40*). A review of the literature reveals that four classes of analgesic manipulations can be identified. The criteria used to classify analgesia as opiate include naloxone reversibility and cross-tolerance to morphine. Hormonal analgesia is attenuated by adrenalectomy, adrenal demedullation, or hypophysectomy. These latter criteria were chosen since all environmental stimuli which produce analgesia activate the pituitary–adrenal cortical and sympathetic–adrenal medullary axes. Brain stimulation is listed in two classes since it can apparently activate both opiate and nonopiate pain inhibitory pathways. The most comprehensive data on the neural substrates of these various analgesic responses are available on the effect of lesions of the DLF, nucleus raphe alatus (NRA), and periaqueductal gray (PAG). Since DLF lesions attenuate all analgesic manipulations tested, the DLF may form the final common pathway for endogenous pain inhibitory systems. Symbols: ↑, potentiation; ↓, attenuation; 0, no effect; ?, conflicting data exist indicating either no effect or attenuation; blank, no data are available; •, inappropriate category.

Classes of analgesia	Similarity to opiates			Neural lesions			Endocrine lesions		
	Systemic naloxone	Intrathecal naloxone	Morphine tolerance (cross-tolerance)	DLF	NRA	PAG	Adrenalectomy	Adrenal demedullation	Hypophysectomy
Neural-opiate									
Brief front paw shock	↓	↓	↓	↓	↓	0	↑		0
Conditioning to footshock	↓	↓	↓	↓	↓	↓	↑		0
Systemic morphine	↓	↓	↓	↓	?	?	↑	0	↑
Intracerebral morphine	↓	?	↓	↓	↓	?	0	•	0
Intrathecal morphine	↓	↓	↓	•	•	•	•	•	•
Brain stimulation	↓		↓	↓	?	?			
Hormonal-opiate									
Acupuncture	↓		0	↓	↓				↓
Prolonged four paw shock	↓		↓				↓	↓	↓
Immobilization	↓								↓
Neural-nonopiate									
Brief hind paw shock	0	0	0	↓	?	0	0		0
Brief four paw shock	0		0				0	0	↑
2-Deoxy-D-glucose	?		↓			0			0
Brain stimulation	0		0	↓	?	?			
Hormonal-nonopiate									
Cold water swims	0		0						↓
Insulin									↓
Unknown-opiate									
Transcutaneous nerve stimulation (low frequency, high intensity)	↓								
Food deprivation	↓								
Unknown-nonopiate									
Transcutaneous nerve stimulation (high frequency, low intensity)	0								
Hypnosis	0								

volves clinical manipulations that attempt to activate pain-inhibitory systems. We will first examine whether these systems are tonically active and then consider the involvement of opiate and nonopiate analgesia systems in acupuncture, transcutaneous electrical nerve stimulation, hypnosis, and placebo effects.

Attempts have been made to determine whether pain-modulatory systems are tonically active. All of these studies have examined the effect of opiate antagonists on pain perception. These data reflect only on the potential involvement of opiate systems. Involvement of nonopiate systems cannot yet be assessed, since the pharmacological bases of nonopiate analgesia are not understood.

The assumption made by these studies has been that administration of opiate antagonists should alter the perception of pain if opiate systems are tonically active (*26, 27*). This change in pain perception would be recorded either as a decreased pain threshold or an increased level of ongoing pain. In general, however, naloxone has failed to affect pain thresholds of normal human volunteers (*42, 43*). In contrast to these negative results, Buchsbaum *et al.* found that naloxone lowered the thresholds of subjects with naturally high pain thresholds, yet had no effect in subjects with low pain thresholds (*44*).

Naloxone does appear to increase pain when delivered to experimental subjects who are already experiencing some level of clinical pain (*45, 46*). Therefore, in this situation, spontaneous activity of an endogenous opiate analgesia system occurs. Ongoing pain is one factor that seems to activate this system. In this regard, these results are consistent with animal studies in which pain activated endogenous analgesia systems.

Clinical pain is treated with diverse manipulations. Most were developed before the recent explosion of information about endogenous pain control systems. Indeed, many evolved from theoretical approaches that are now outdated or incorrect. Nevertheless, the procedures are useful, and it may be informative to reexamine them in the light of current knowledge.

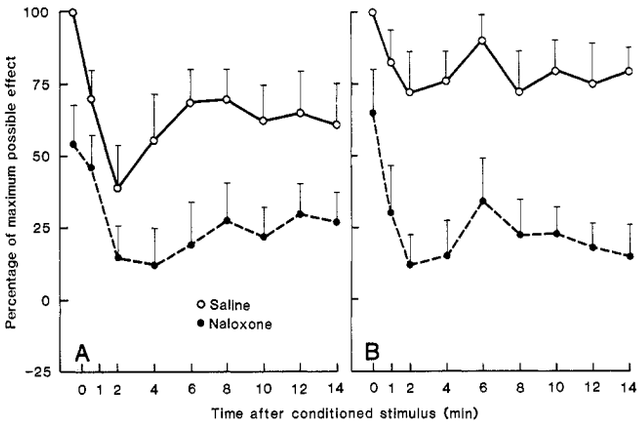


Fig. 7. Effect of systemic naloxone on classically conditioned analgesia. A nonelectrified grid was the conditioned stimulus, either brief front paw (A) or hind paw (B) shock was the unconditioned stimulus, and analgesia was the unconditioned response. After conditioning, potent analgesia was elicited by placing the animals on the nonelectrified grid. Classically conditioned analgesia was antagonized by systemic naloxone, regardless of whether front paw or hind paw shock was delivered during conditioning. These data, in addition to the observation that classically conditioned analgesia shows cross-tolerance to morphine, indicate that the animals learn to activate endogenous opiate systems.

Counterirritation, Acupuncture, and Transcutaneous Nerve Stimulation

The belief that counterirritation—an acute, painful stimulus—can be used to alleviate ongoing pain has been held since antiquity (*47*). This procedure has a great deal in common with acupuncture and transcutaneous nerve stimulation. All use the application of somatic stimuli, either noxious or innocuous, to obtain relief from pain. A reliable characteristic of the pain relief produced by these procedures is that it persists beyond the period of treatment. The site of treatment in relation to the painful area is variable, ranging from the painful dermatome itself to a theoretically unpredictable constellation of points in classical Chinese acupuncture. The duration of treatment varies from less than a minute to hours. All of these factors are important determinants of the effects produced by footshock in animals. Thus, the highly variable effects observed in the clinic would be predicted from animal research. Nevertheless, human data suggest the involvement of the systems described above.

The involvement of an opiate system in these analgesias was, to our knowledge, first suggested by Mayer *et al.* (*10, 43*), who showed that the increased pain thresholds produced by traditional acupuncture in human subjects could be completely reversed by naloxone. Other investigators (*48, 49*) found that naloxone only partially reduced electroacupuncture analgesia. The differences in the magnitude of the effects seen in these studies are enlightening when animal studies described above are considered. Mayer *et al.* (*10, 43*) used the ho-ku points in the hands to induce analgesia in the teeth, acupuncture points far removed from the painful region. In contrast, Chapman and Benedetti (*48*) stimulated the face to produce analgesia in the teeth and saw only a small effect of naloxone. Thus, it seems likely that, as in animal experiments, stimulation of regions adjacent to the painful area activates nonopiate analgesia systems, whereas stimulation of distant dermatomes activates opiate systems.

Other variables of stimulation also seem critical in determining whether opiate or nonopiate systems are involved. Sjölund and Eriksson (*49*) have shown that high-frequency–low-intensity and low-frequency–high-intensity nerve stimulation can both alleviate clinical pain. However, only the analgesia produced by low-frequency–high-intensity stimulation could be reversed by naloxone. From this work, it seems that noxious stimulation is required for the activation of opiate inhibitory systems. In fact, that acupuncture and transcutaneous nerve stimulation should be painful to produce maximal effects has been pointed out (*50*).

Acupuncture and transcutaneous stimulation seem to be forms of counterirritation activating both opiate and nonopiate systems. The variable clinical outcomes observed probably result from differential recruitment of segmental, extrasegmental, opiate, and nonopiate pain-inhibitory systems, all of which are now known to be activated by these types of stimulation in animals.

Hypnosis and Placebo Analgesia

Until recently, the neural mechanisms underlying the pain-alleviating effects of hypnosis and placebo were attributed to mysterious or psychological processes. The uncovering of neural systems that modulate pain transmission, however, has led to some attempt to integrate these phenomena into a scientific framework.

The neural mechanisms involved in hypnotic analgesia present a difficult

problem for analysis since hypnosis is probably a uniquely human phenomenon. This severely restricts the experimental manipulations used to study it. Nevertheless, some progress has been made in evaluating the role of opiate analgesia systems in hypnotic analgesia. The approach has been to administer naloxone to humans in whom hypnotic analgesia has been induced. Presumably, if an opiate mechanism mediates analgesia, naloxone should reverse the effect. Two independent attempts to reverse hypnotic analgesia with naloxone have failed (*51, 52*). In one of these, Barber and Mayer (*51*) followed a procedure identical to one in which acupuncture analgesia was reversed by naloxone (*43*). Thus, hypnosis seems to differ from acupuncture, and it induces its effects through nonopiate mechanisms.

Naloxone has also been used to examine whether endogenous opiates are involved in placebo analgesia. Levine and co-workers (*46*) reported that naloxone antagonized placebo effects. Although this conclusion has been questioned on technical grounds (*53*), to our knowledge, no conflicting data have been published. The possibility that opiates are involved in some aspect of placebo analgesia seems reasonable since footshock analgesia can be classically conditioned in rats. Placebo analgesia can be conceived of as a classical conditioning procedure wherein the placebo manipulation (injections, pills) is the CS and prior medication or treatment is the UCS.

Although explanations of this sort are speculative, they indicate the wealth of concepts from experimental pain research now available for clinical evaluation. Our increasing knowledge of pain-modulatory systems has the potential not only of providing explanations of current therapies but of suggesting new approaches to control pain. The preponderance of current pain therapies involve either the surgical destruction of neural tissue or the use of addictive drugs. Such procedures offer difficulties for the prolonged treatment of chronic pain. If multiple pain-inhibitory systems could be activated pharmacologically or otherwise in an alternating sequence, the problems of tissue destruction and addiction could be circumvented.

References and Notes

1. D. J. Mayer, in *Pain, Discomfort and Humanitarian Care*, L. K. Y. Ng and J. J. Bonica, Eds. (Elsevier/North-Holland, Amsterdam, 1980), pp. 83–105; H. L. Fields and A. I. Basbaum, *Annu. Rev. Physiol.* **40**, 217 (1978).
2. W. Noordenbos, *Pain* (Elsevier, Amsterdam, 1959); R. Melzack and P. D. Wall, *Science* **150**, 971 (1965).
3. D. V. Reynolds, *Science* **164**, 444 (1969); D. J. Mayer, T. L. Wolfle, H. Akil, B. Carder, J. C. Liebeskind, *ibid.* **174**, 1351 (1971).
4. J. C. Yeung, T. L. Yaksh, T. A. Rudy, *Pain* **4**, 23 (1977). Subsequent studies have revealed that stimulation of or morphine microinjection into other neural areas can produce analgesia as well. For detailed discussion of the neural bases of morphine and stimulation-produced analgesia, see (*1*).
5. R. Murfin, G. J. Bennett, D. J. Mayer, *Soc. Neurosci. Abstr.* **2**, 946 (1976); A. I. Basbaum, N. J. E. Marley, J. O'Keefe, C. H. Clanton, *Pain* **3**, 43 (1977). The descending DLF axons involved in pain inhibition arise, at least in part, in the nucleus raphe magnus and the surrounding nucleus reticularis paragigantocellularis (*1, 31*).
6. G. J. Bennett and D. J. Mayer, *Brain Res.* **172**, 243 (1979).
7. R. Samanin and L. Valzelli, *Eur. J. Pharmacol.* **16**, 298 (1971).
8. D. J. Mayer and R. L. Hayes, *Science* **188**, 941 (1975); B. J. Sessle, R. Dubner, L. F. Greenwood, G. E. Lucier, *Can. J. Pharmacol. Physiol.* **54**, 66 (1975).
9. H. Akil, D. J. Mayer, J. C. Liebeskind, *Science* **191**, 961 (1976).
10. D. J. Mayer, *Neurosci. Res. Prog. Bull.* **13**, 94 (1975).
11. J. Hughes, *ibid.*, p. 55.
12. C. B. Pert and S. H. Snyder, *Science* **179**, 1011 (1973); J. M. Hiller, J. Pearson, E. J. Simon, *Res. Commun. Chem. Pathol. Pharmacol.* **6**, 1052 (1973); L. Terenius, *Acta Pharmacol. Toxicol.* **32**, 317 (1973).
13. C. B. Pert, A. M. Snowman, S. H. Snyder, *Brain Res.* **70**, 184 (1974).
14. C. B. Pert, M. J. Kuhar, S. H. Snyder, *Life Sci.* **16**, 1849 (1975).
15. J. Hughes and H. W. Kosterlitz, paper presented at a Neuroscience Research Program Workshop, Boston, Mass., 19 to 21 May 1974.
16. M. W. Adler, *Life Sci.* **26**, 497 (1980).
17. J. Hughes, *Brain Res.* **88**, 295 (1975).
18. R. L. Hayes, G. J. Bennett, P. Newlon, D. J. Mayer, *Soc. Neurosci. Abstr.* **2**, 939 (1976); *Brain Res.* **155**, 69 (1978); R. L. Hayes, D. D. Price, G. J. Bennett, G. L. Wilcox, D. J. Mayer, *ibid.*, p. 91.
19. D. J. Mayer and L. R. Watkins, in *Modern Problems of Pharmacopsychiatry: The Role of Endorphins in Neuropsychiatry*, H. E. Emrich, Ed. (Karger, Basel, 1981), pp. 68–96.
20. H. Akil, J. Madden, R. L. Patrick, J. D. Barchas, in *Opiates and Endogenous Opioid Peptides*, H. W. Kosterlitz, Ed. (North-Holland, Amsterdam, 1976), pp. 63–70; J. Madden, H. Akil, R. L. Patrick, J. D. Barchas, *Nature (London)* **265**, 358 (1977).
21. G. H. DeVries, W. T. Chance, W. R. Payne, J. A. Rosecrans, *Pharmacol. Biochem. Rev.* **11**, 741 (1979); W. T. Chance, *Neurosci. Biobehav. Rev.* **4**, 55 (1979).
22. J. W. Lewis, J. T. Cannon, J. C. Liebeskind, *Science* **208**, 623 (1980).
23. D. A. Cobelli, L. R. Watkins, D. J. Mayer, *Soc. Neurosci. Abstr.* **6**, 247 (1980). The tail-flick test measures the latency between the onset of a radiant source focused on the tail and the occurrence of a spinally mediated tail flexion. This reflexive response provides a reliable measure of pain threshold. The degree of analgesia produced by footshock was calculated as a percentage of the maximal possible effect according to the following equation: $[(TL - BL)/(8.0 - BL)] \times 100$, where BL is the baseline tail-flick latency (approximately 3.5 to 4.0 seconds), TL is the test latency (tail-flick latency measured after footshock), and 8.0 is the maximum latency possible. (The trial was terminated at 8 seconds if no tail flick occurred, in order to prevent tissue damage.) The degree of inhibition of the tail-flick reflex by various drugs has proven to be a highly reliable predictor of the drugs' analgesic potency in humans [L. Grumbach, *Henry Ford Hosp. Int. Symp.* **15**, 163 (1966)]. We have previously examined FSIA across a variety of behavioral assays and have reliably observed potent pain inhibition in all cases (*18*). For simplicity, we have chosen to use the tail-flick test in every experiment in order to aid in the comparison of results.
24. In all of our work on front paw FSIA, hind paw FSIA, and classically conditioned analgesia, the experimenter was unaware of the drug or surgical manipulation being tested.
25. L. R. Watkins, D. A. Cobelli, P. Faris, M. D. Aceto, D. J. Mayer, *Brain Res.*, in press.
26. R. Hayes, D. D. Price, R. Dubner, *Science* **196**, 600 (1977).
27. A. Pert and M. Walter, *Life Sci.* **19**, 1023 (1976).
28. D. G. Teiger, *J. Pharmacol. Exp. Ther.* **190**, 408 (1974).
29. L. R. Watkins, D. A. Cobelli, H. H. Newsome, D. J. Mayer, *Brain Res.*, in press.
30. L. R. Watkins, D. A. Cobelli, D. J. Mayer, *ibid.*, in press.
31. L. R. Watkins, G. Griffin, G. R. Leichnetz, D. J. Mayer, *ibid.* **181**, 1 (1980).
32. E. G. Young, L. R. Watkins, D. J. Mayer, *Soc. Neurosci. Abstr.* **7**, 533 (1981).
33. L. R. Watkins, E. G. Young, I. B. Kinscheck, D. J. Mayer, *ibid.*, p. 340.
34. L. R. Watkins and D. J. Mayer, *Brain Res.*, in press.
35. This effect appears to be Pavlovian classical conditioning since the analgesic effect extinguishes and cannot be explained by sensitization, pseudoconditioning, or backward conditioning [compare with (*19*)].
36. H. K. Proudfit, *Neuroscience*, in press.
37. H. Akil and D. J. Mayer, *Brain Res.* **44**, 692 (1972); J. L. Oliveras, Y. Hosobuchi, F. Redjemi, G. Guilbaud, J. M. Besson, *ibid.* **120**, 221 (1977).
38. G. J. Prieto, G. J. Giesler, J. T. Cannon, *Soc. Neurosci. Abstr.* **4**, 460 (1979).
39. B. Pomeranz, R. Cheng, P. Law, *Exp. Neurol.* **54**, 172 (1977); J. W. Lewis, E. H. Chudler, J. T. Cannon, J. C. Liebeskind, *Proc. West. Pharmacol. Soc.* **24**, 323 (1981); S. Amir and Z. Amit, *Life Sci.* **24**, 439 (1979).
40. S. Eh, in *National Symposia of Acupuncture and Moxibustion and Acupuncture Anaesthesia* (Beijing, 1979), p. 27.
41. R. J. Bodnar, D. D. Kelly, M. Brutus, M. Glusman, *Neurosci. Biobehav. Rev.* **4**, 87 (1979).
42. A. El-Sobky, J. Dostrovsky, P. D. Wall, *Nature (London)* **263**, 783 (1976); P. Grevert and A. Goldstein, *Science* **199**, 1093 (1978).
43. D. J. Mayer, D. D. Price, A. Rafii, *Brain Res.* **121**, 368 (1977).
44. M. S. Buchsbaum, G. C. Davis, W. E. Bunney, Jr., *Nature (London)* **270**, 620 (1977).
45. L. Lasagna, *Proc. Soc. Exp. Biol. Med.* **58**, 978 (1965).
46. J. D. Levine, N. C. Gordon, H. L. Fields, *Lancet* **1978-II**, 654 (1978); *Nature (London)* **272**, 826 (1978).
47. K. Kane and A. Taub, *Pain* **1**, 125 (1975).
48. C. R. Chapman and C. Benedetti, *Life Sci.* **21**, 1645 (1977).
49. B. H. Sjölund and M. B. E. Eriksson, *Brain Res.* **173**, 295 (1979).
50. E. J. Fox and R. Melzack, *Pain* **2**, 141 (1976); R. Mann, *Br. J. Anaesth.* **46**, 361 (1974); R. Melzack, *Pain* **1**, 357 (1975).
51. J. Barber and D. J. Mayer, *Pain* **4**, 41 (1977).
52. A. Goldstein and E. F. Hilgard, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 2041 (1975).
53. A. D. Korczyn, *Lancet* **1978-II**, 1304 (1978).

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