

# Mechanisms of Acupuncture Analgesia Produced by Low Frequency Electrical Stimulation of Acupuncture Points

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## 2.1

### Introduction

Three noteworthy phenomena have been recognized in surgical acupuncture analgesia (AA) produced by low frequency electrical stimulation of acupuncture points: (1) consciousness is maintained, allowing the patient to talk during surgery, (2) stimulation of specific acupuncture points is essential to maintain analgesia, and (3) analgesia persists long after stimulation has been terminated, allowing the patient to move without pain after surgery. The mechanisms by which AA is produced might be clarified by investigating these phenomena. This review will explore possible mechanisms based on results from animal experiments.

Consciousness depends on activation of the brainstem ascending reticular activating system (RAS) that produces widespread stimulation of the cerebral cortex and maintains consciousness nonspecifically through the reticular nucleus in the thalamus. The RAS is activated by collateral pathways that diverge from each specific sensory afferent pathway projecting to each sensory cortex. Neurophysiological research has shown that anesthetic drugs used during surgical operations inhibit activity of the RAS. Since consciousness is diminished under this condition, sensory information reaching the sensory cortex is not translated into perception. On the other hand, it is also commonly observed that normally painful stimuli are suppressed on the battlefield and during aggressive sports such as rugby. Such analgesia is thought to be brought about by activation of the descending pain inhibitory system (DPIS) originating from the limbic system and which blocks pain information as it enters the central nervous system. Consciousness can thus be maintained in such a condition. If stimulation of a specific acupuncture point activates the DPIS through a particular pathway connected to the brain system which suppresses pain, it can be assumed that AA is produced by activation of the DPIS. This assumption has been examined in our laboratories using several animal experiments.

## 2.2

### Classification of Acupuncture Afferent and Efferent Pathways for Producing Acupuncture Analgesia [11–13, 16, 22, 23]

The neuronal structures comprising the AA-producing brain pathway can be identified when microelectrode stimulation induces analgesia in a manner that mimics AA and by tissue ablation that results in subsequent blockage of AA. However, the nature

of the analgesia produced depends upon the brain areas stimulated and can be classified into two categories. The first category includes analgesia that is naloxone-reversible, disappears after hypophysectomy, persists long after stimulation of the acupoint is terminated, and exhibits individual variation in effectiveness. These features are similar to those of AA. In this category, brain potentials are evoked by stimulation of acupoints in the same areas that produce analgesia. Stimulation of brain areas associated with the second category produces analgesia that is not naloxone-reversible, not affected by hypophysectomy, is produced only during stimulation, and exhibits no individual variation in effectiveness. Evoked potentials are not obtained from brain regions producing analgesia of this second category, but nonsynchronized neuronal activities are obtained by stimulation of acupoints [16].

Brain regions producing analgesia of the first category appear to comprise an afferent pathway for acupuncture, since the pituitary gland is involved in this analgesia and electrical potentials are evoked in these brain regions by stimulation of acupoints. Similarly, areas producing analgesia related to the second category appear to comprise an efferent pathway for acupuncture, since the pituitary gland is not involved and synchronized electrical potentials are not evoked in these regions by stimulation of acupoints [12, 16, 19]. All brain regions producing analgesia associated with the second category seem to be connected to the DPIS; AA is produced by activation of the DPIS, which is excited by stimulation of specific acupoints through a particular pathway connected to the DPIS. This DPIS-producing analgesia related to the second category is defined as the acupuncture *efferent* pathway, whereas the particular pathway from specific acupoints to the DPIS is defined as the acupuncture *afferent* pathway.

### 2.2.1

#### Acupuncture Efferent Pathway [13, 16, 24]

Acupuncture analgesia can be abolished by concurrent lesions of the Raphe nucleus and the reticular paragigantocellular nucleus that are known as the origins of the serotonergic and the noradrenergic descending pain-inhibitory systems. Stimulation of these nuclei respectively produces serotonergic and noradrenergic analgesia of the second category. The final production of AA is induced by activation of these descending pain inhibitory systems. The descending pain inhibitory pathway serves as the acupuncture efferent pathway from the hypothalamic ventromedian nucleus (HVM); it is divided into two parts that connect to the descending serotonergic and noradrenergic systems. The posterior part of the hypothalamic arcuate nucleus (P-HARN) is anatomically connected to the HVM. Analgesia produced by stimulation of both the HVM and the P-HARN is associated with the second category. Synaptic transmission from the P-HARN to the HVM is apparently dopaminergic, since analgesia produced by stimulation of the P-HARN is blocked by lesions of the HVM or by dopamine antagonists (Fig. 1).

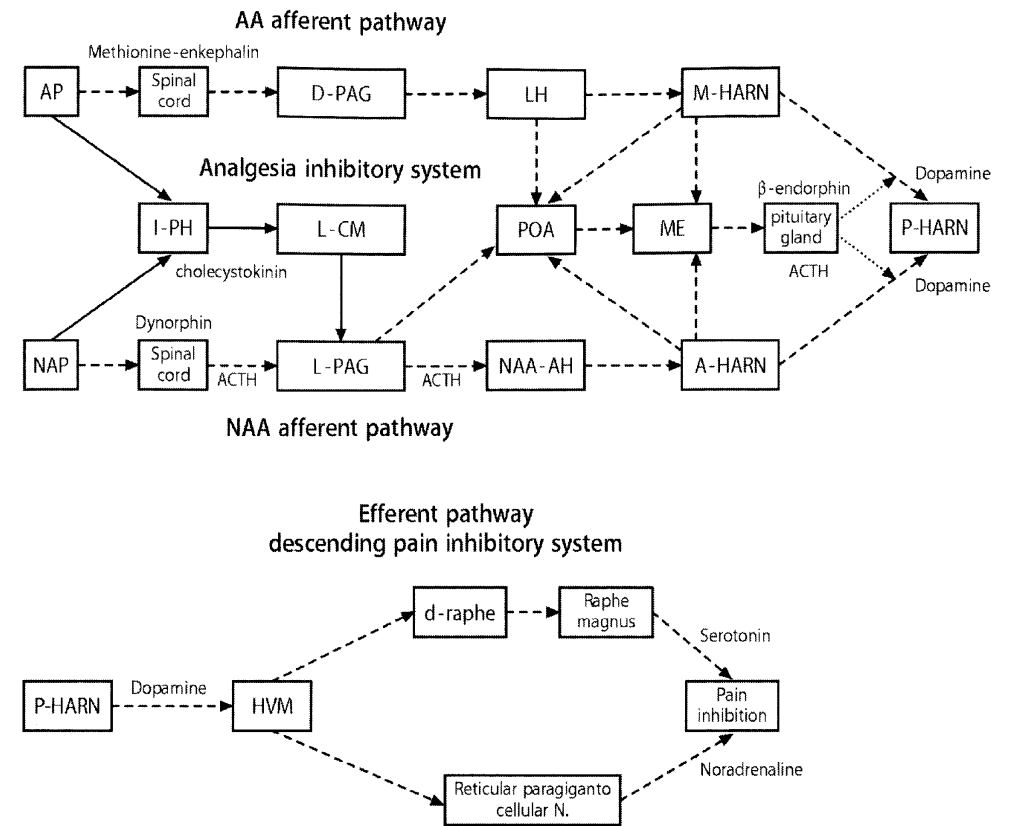


Fig. 1. Transmitters in the afferent pathway in both AA and non-AA, in the analgesia inhibitory system (upper figure), and in the acupuncture efferent pathway as the descending pain inhibitory systems (bottom figure). AP acupuncture point, D-PAG dorsal periaqueductal central gray, L-PAG lateral periaqueductal central gray, LH lateral hypothalamus, ME median eminence, M-HARN, A-HARN, P-HARN medial, anterior, and posterior hypothalamic arcuate nucleus, NAP nonacupuncture point, NAA-AH anterior hypothalamus in the NAA afferent pathway, POA preoptic area, I-PH inferior posterior hypothalamus, L-CM lateral centromedian nucleus of thalamus

### 2.2.2

#### Acupuncture Afferent Pathway [11, 12, 23]

The acupuncture afferent pathway (Fig. 1) starts from an acupoint, ascends through the contralateral anterolateral tract to the dorsal periaqueductal central gray, and reaches the medial part of the hypothalamic arcuate nucleus (M-HARN). Brain regions belonging to the AA afferent pathway can be identified by exhibition of analgesia of the first group related to anatomically known connections. The rostral and caudal relations between these regions have been identified by the loss of stimulation-produced analgesia of the caudal region that follows lesions of the rostral region. These relations are shown in Figs. 1 and 2 [23].

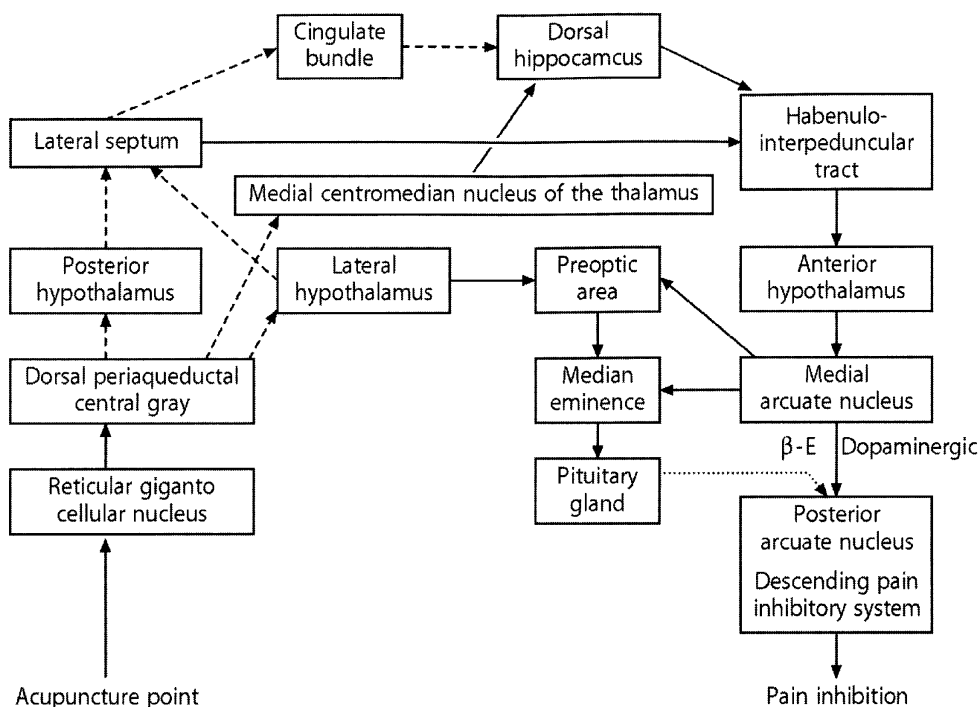
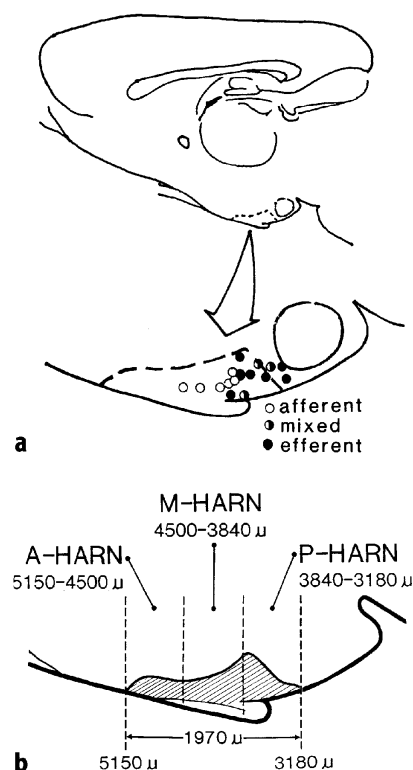


Fig. 2. Acupuncture analgesia-producing system

Fig. 3a, b. Location of lesioned and stimulated sites in the arcuate nucleus. The arcuate nucleus is bounded by the broken line. The enlarged figure shows the sites at which lesions abolished AA. Analgesia produced by stimulation (SPA) at the open circles was abolished by hypophysectomy. Afferent SPA at the filled circles was not affected by hypophysectomy. Efferent SPA at the half-filled circles was partially abolished by hypophysectomy. The hypothalamic arcuate nucleus (HARN) indicated by oblique lines was divided into three equal parts: anterior (A-HARN), medial (M-HARN), and posterior (P-HARN)



### 2.2.3

#### Synaptic Connections Between Acupuncture Afferent and Efferent Pathways [25, 28]

The final region of the acupuncture afferent pathway is found in the M-HARN, which is anatomically close to the P-HARN, the initial region of the acupuncture efferent pathway (Fig. 3). Microinjection of the dopamine antagonist haloperidol antagonizes AA dose-dependently, while microinjection of dopamine into the P-HARN induces dose-dependent analgesia. Dopamine thus seems to serve as the neurotransmitter between the M-HARN and the P-HARN, i.e., as the neurotransmitter at the interface between the acupuncture afferent and efferent pathways. This possibility is further supported by neuronal activity in the P-HARN. Neurons in the P-HARN that respond to acupoint stimulation also respond to iontophoretically administered dopamine, whereas neurons in the P-HARN that do not respond to acupoint stimulation also do not respond to iontophoretically administered dopamine [25] (Fig. 4).

A branch of the acupuncture afferent pathway ascending to the M-HARN diverges at the lateral hypothalamus (LH) to reach the pituitary gland. Lesions of brain nuclei near this pathway to the pituitary, e.g., the preoptic area (POA) or the median eminence (ME), abolish AA. Electrical potentials are evoked in these brain areas by stimulation of acupoints, but stimulation of these particular brain structures does not produce analgesia [25, 28] (Figs. 1, 2, 5). Since acupuncture analgesia and pain relief produced by stimulation of the acupuncture afferent pathway to the M-HARN are both abolished by hypophysectomy,  $\beta$ -endorphin released from the pituitary gland may play an essential role in dopaminergic transmission in the P-HARN [25] (Fig. 5). Microinjection of naloxone to the P-HARN antagonizes AA dose-dependently and microinjection of  $\beta$ -endorphin or morphine produces analgesia dose-dependently. Analgesia produced by microinjection of  $\beta$ -endorphin disappears after denervation of the M-HARN, but analgesia produced by microinjection of dopamine to the P-HARN remains [25] (Fig. 6). These findings suggest that  $\beta$ -endorphin might act

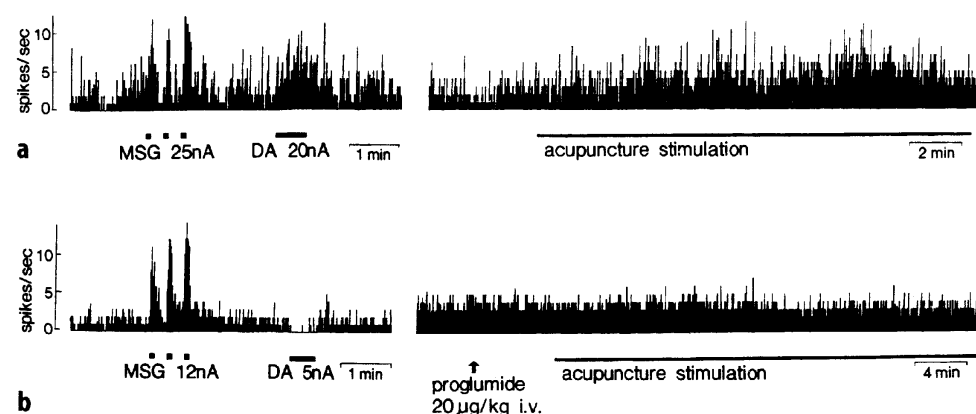
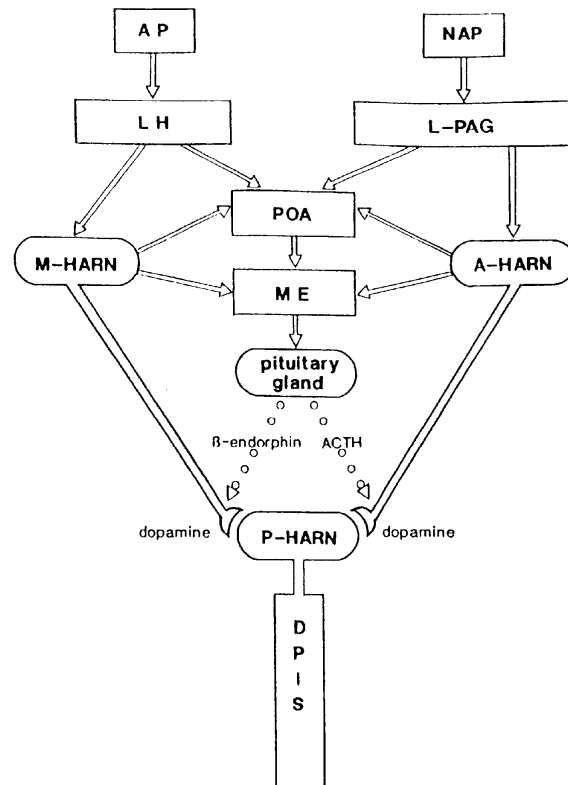


Fig. 4a, b. Rate histograms of two different typical P-HARN neurons in acupuncture-responder rats. One was excited by iontophoretically applied 25 nM monosodium glutamate (MSG) and 20 nM dopamine (DA), and also by acupuncture stimulation. The other was excited by iontophoretically applied 12 nM MSG but inhibited by 5 nM DA and did not respond to acupuncture stimulation, even after IV 20 mg/kg progulimide

Fig. 5. Synaptic transmission between M-HARN and P-HARN in AA and that between A-HARN and P-HARN in non-AA. Two pathways diverge from the lateral hypothalamus (*LH*) in AA and from the L-PAG in non-AA. Both AA and non-AA are carried by dopaminergic transmission to the P-HARN. Other paths associated with release from the pituitary gland of  $\beta$ -endorphin (in AA) and ACTH (in non-AA) modulate the dopaminergic systems in the synapse to the P-HARN that is the initial region of the descending pain inhibitory system (*DPIS*). Convergence is necessary to activate the preoptic area (*POA*) and median eminence (*ME*). Hypophysectomy abolished analgesia produced by stimulation of M-HARN and A-HARN. Stimulation of the POA or the ME did not produce analgesia



presynaptically at dopaminergic synapses in the P-HARN. This notion is further supported by the activity of P-HARN neurons. Neuronal activity in the P-HARN that occurs in response to acupuncture stimulation is not affected by iontophoretic administration of morphine or ultramicroinjection of  $\beta$ -endorphin via picospritzer [22] (Fig. 7).

Since morphine and  $\beta$ -endorphin act similarly in the P-HARN,  $\beta$ -endorphin released from the pituitary gland might be the neurohumoral factor acting presynaptically on axon terminals of the M-HARN neurons that innervate P-HARN neurons. Although  $\beta$ -endorphin microinjected into the P-HARN produces analgesia, electrical stimulation of the POA or ME in the pathway to the pituitary gland does not. Therefore, the amount of  $\beta$ -endorphin released by such stimulation is not sufficient to activate the P-HARN neurons without afferent impulse from the M-HARN. Morphine and  $\beta$ -endorphin might also act in other areas of the AA afferent pathway. This possibility was explored by recording electrical potentials evoked by stimulation of the acupoint in the final station of the AA afferent pathway, the M-HARN. Such potentials are enhanced by intravenously administered morphine (0.5 mg/kg) and abolished by hypophysectomy. The abolished evoked potentials are temporarily restored by morphine [12] (Fig. 8). Therefore, sites responsive to  $\beta$ -endorphin released from the pituitary gland might be widespread in the AA afferent pathway. Opioid receptors have also been reported in many regions of the acupuncture afferent pathway [1, 5, 10].

Fig. 6. Dose-dependence of analgesia caused by micro-injection of dopamine and  $\beta$ -endorphin into the P-HARN, and effects of denervation of the M-HARN on this dose-dependence. Upper control, lower after denervation of the M-HARN

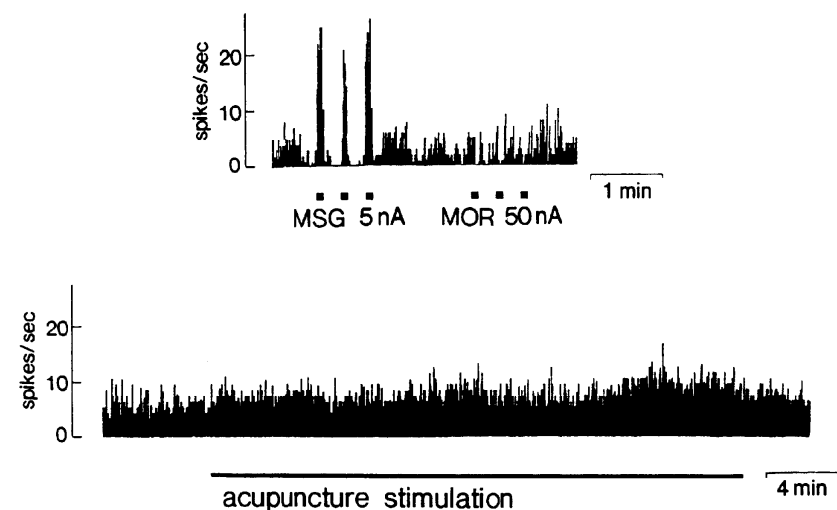
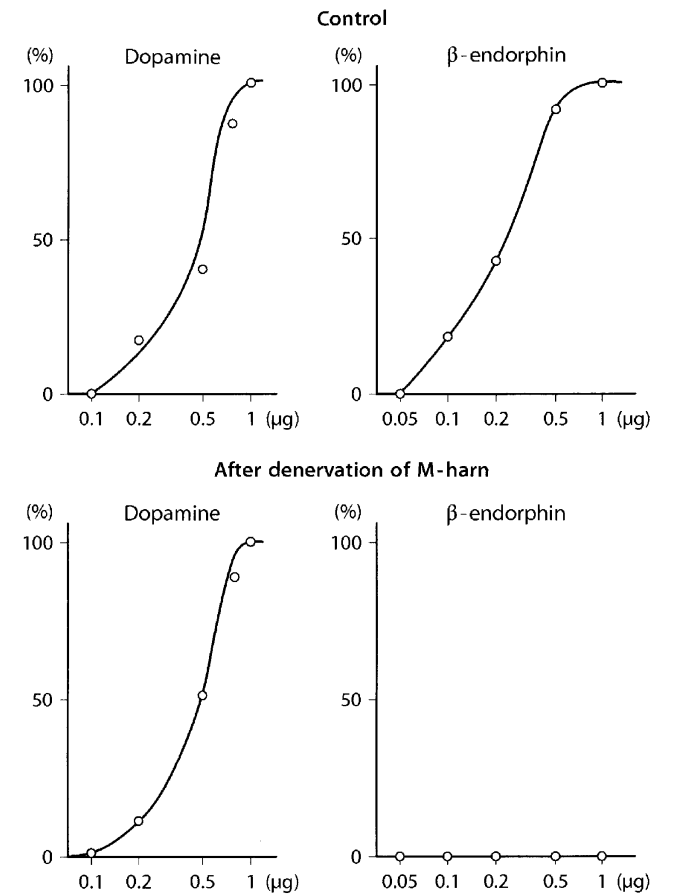
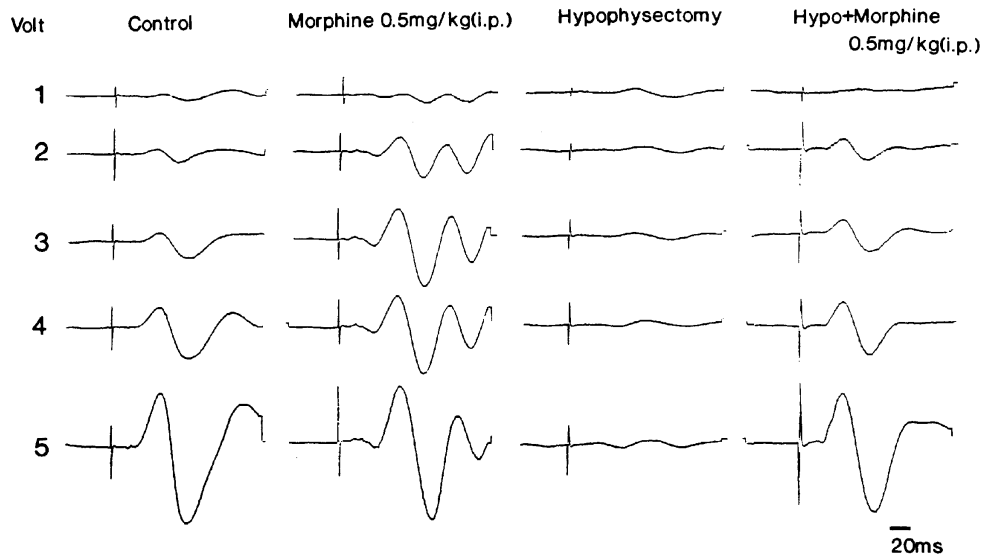


Fig. 7. Rate histograms showing typical P-HARN neuron responses in an acupuncture responder rat. The P-HARN neuron excited by iontophoretic 5 nA monosodium glutamate (MSG) did not respond to iontophoretically applied 50 nA morphine (Mor) but was excited by acupuncture stimulation (bottom record)



**Fig. 8.** Effects of hypophysectomy and morphine on potentials evoked in the M-HARN by stimulation of an acupuncture point (AP). *Column 1* Control. Evoked potential increased with increasing stimulus. *Column 2* Effect of intraperitoneal 0.5 mg/kg morphine on potentials 20 min after application and with 5 min intervals between successive stimuli. *Column 3* Effect of hypophysectomy on potentials. *Column 4* Effect of IP 0.5 mg/kg morphine on potentials after hypophysectomy. Note close similarity to column 1. Voltage (at 0.05 ms duration) indicated by number at left applies to all columns

### 2.3

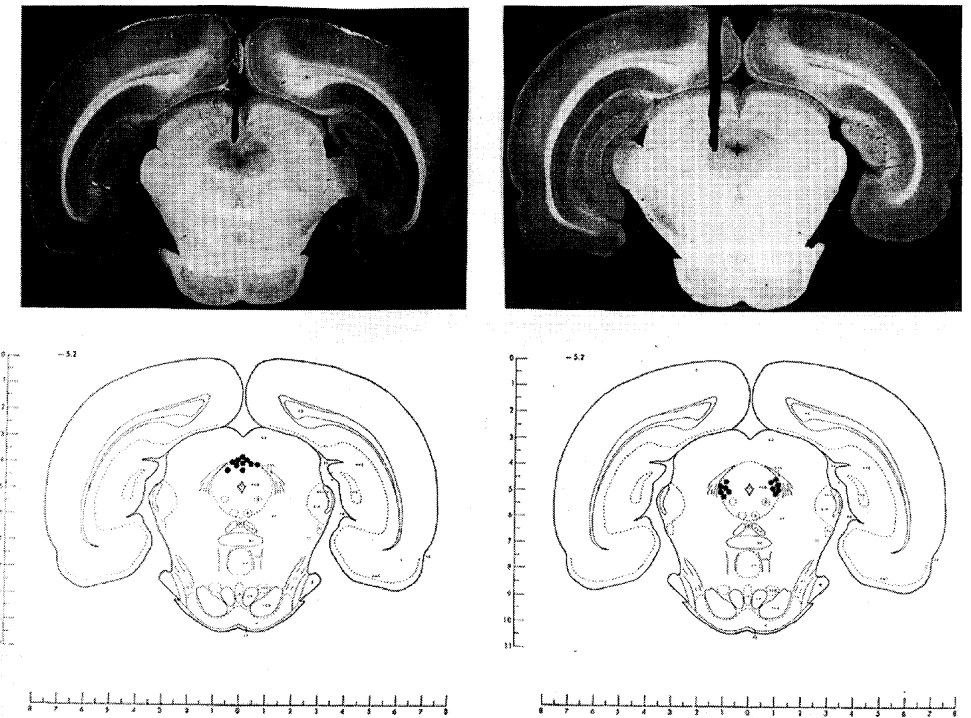
#### Stimulation of Specific Acupoints for the Production of AA [23]

Low frequency (1 Hz) electrical stimulation of the first dorsal finger muscle and the anterior tibial muscle in rats [11, 23], which correspond to the muscles underlying the human LI.4 (Hegu) and St.36 (Zusanli) acupoints, produces behavioral analgesia, evaluated in rats by tail flick latency. The intensity of electrical stimulation must be sufficient to cause muscle contraction in order to obtain AA. In contrast, stimulation of other muscles does not produce behavioral analgesia. Hence, the Hegu and Zusanli acupoints seem uniquely able to activate the DPIS through the particular pathway connected to the DPIS [3].

### 2.4

#### Differentiation of Acupoints and Nonacupoints by Responses of Central Neuronal Structures [11, 14, 15, 17, 18]

Potentials can be evoked specifically in the bilateral dorsal areas of the periaqueductal central gray (D-PAG) by stimulating the muscles underlying the Hegu and Zusanli acupoints but not by stimulation of other muscles (Fig. 9). Lesions of the D-PAG abolish AA. Microelectrode stimulation of this region produces analgesia of the first category that can be reversed by either naloxone or hypophysectomy. Stimulation of the auricular levator muscle beneath the X18 (Chihmo) acupoint in rabbits elicits evokes potentials in the D-PAG [11, 23]. Stimulus conditions as stated above which lead to



**Fig. 9.** Examples of scars produced by electrodes inserted into the D-PAG (upper left) and L-PAG (upper right). Sites of recordings in the D-PAG (lower left) and L-PAG (lower right)

AA were confirmed by potentials in the D-PAG. Therefore, only three acupoints for producing AA have been identified: Hegu, Zusanli, and Chihmo.

Stimulation of muscles including those beneath Hegu and Zusanli also produces *nonspecific* potentials bilaterally in the *lateral* parts of the periaqueductal central gray (L-PAG) [17] (Fig. 9). Potentials in the L-PAG are gradually decreased by repetitive 1 Hz stimulation of these muscles and disappear completely 10 minutes after the onset of stimulation [15, 17] (Fig. 10). Hence, potentials in the L-PAG are inhibited by such stimulation in a self-inhibiting fashion. Lesions of the L-PAG do not affect AA, but analgesia is produced by stimulation of the rostral L-PAG. This analgesia is largely reversible with dexamethasone, and the dexamethasone-insensitive portion is readily blocked by naloxone or hypophysectomy. Hence, acupoints are connected via the D-PAG to the particular pathway that is not self-inhibited during the production of AA. On the other hand, both acupoints and nonacupoints are connected nonspecifically to the other, self-inhibiting pathway via the L-PAG. The latter brain region belongs to a pathway distinct from the AA afferent pathway, whose analgesia production is self-inhibiting (Fig. 11). These results imply that acupoints and nonacupoints can be differentiated by their connections with different analgesia-producing central pathways [14, 17] (Figs. 1, 11).

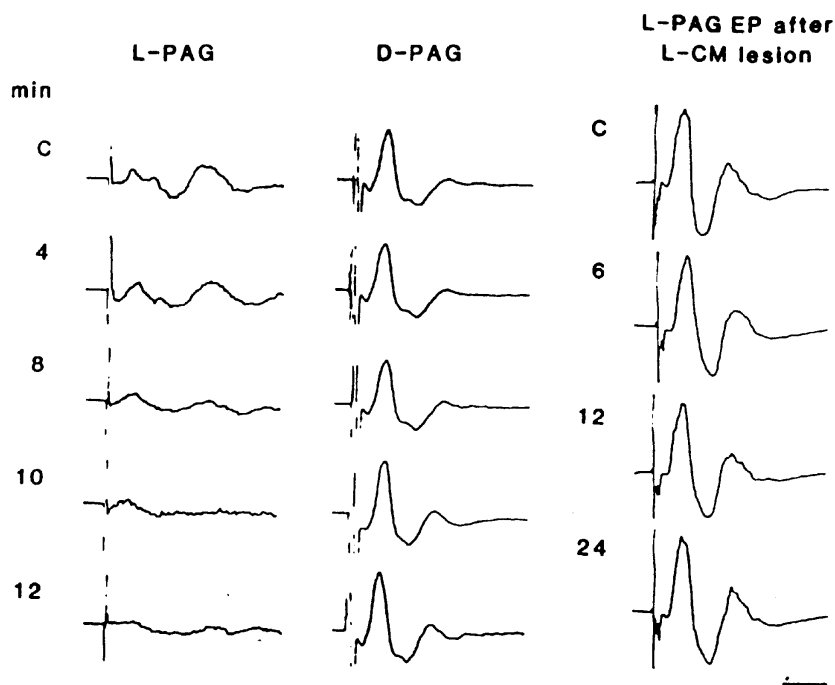


Fig. 10. L-PAG evoked potentials from a typical rat were gradually depressed and finally abolished by repetitive 1 Hz stimulation of the acupuncture points (left). Those in the D-PAG were not influenced (middle). After lesioning the L-CM, inhibition of evoked potentials in the L-PAG disappeared (right). Numbers by each record indicate time in minutes after start of stimulation

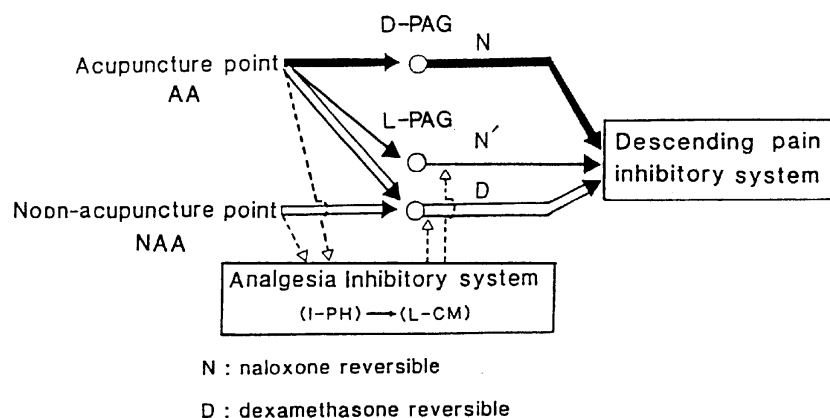


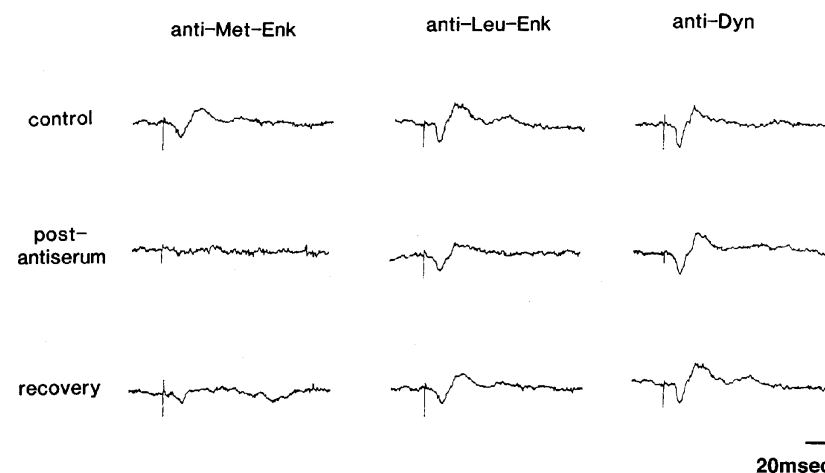
Fig. 11. Differentiation of acupuncture and nonacupuncture points by the analgesia inhibitory system.

2.5

Similarities Between Acupuncture Analgesia and Morphine Analgesia

Analgesia produced by intraperitoneal 0.5 mg/kg morphine is of a similar degree to that produced by low frequency electroacupuncture. In addition, both types of analgesia are abolished by hypophysectomy, lesions of the AA afferent and efferent pathways, naloxone, and antagonists of transmitters involved in the AA efferent pathway. In addition, individual variations in effectiveness between AA and morphine analgesia are highly correlated. Animals can be classified as responders or nonresponders by the presence or absence of a significant increase ( $p < 0.05$ ) in tail flick latency.

Effects of opioid peptides antiserum on d-PAG evoked potential



Effects of opioid peptides antiserum on I-PAG evoked potential

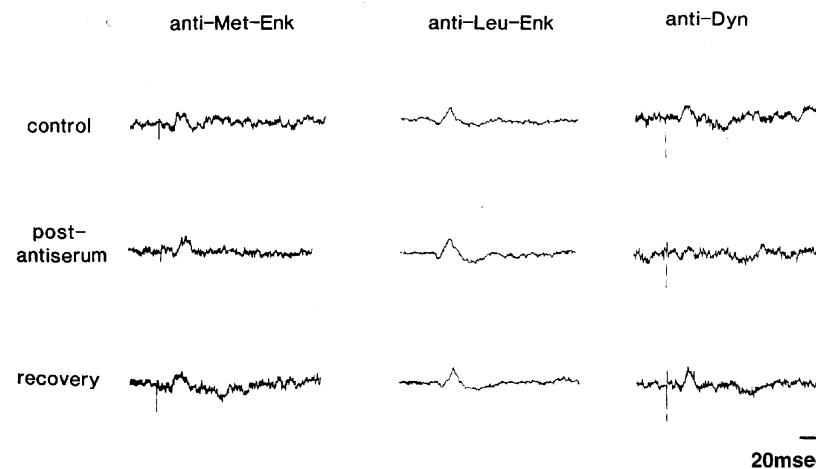


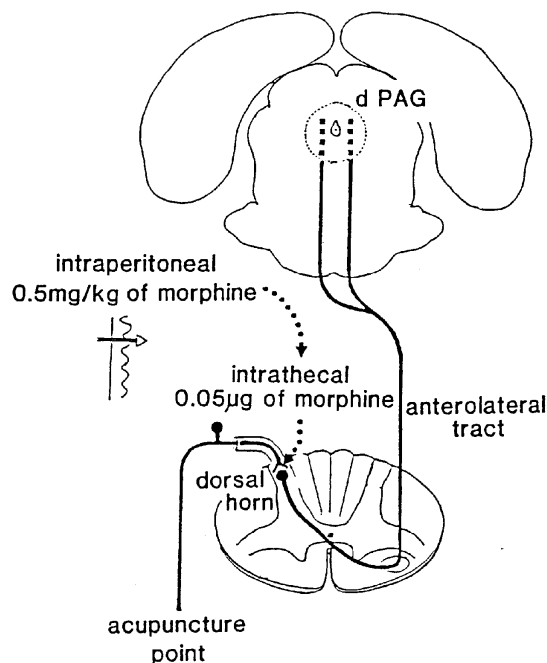
Fig. 12. Effect of intrathecal application of antisera to met-enkephalin (left), leu-enkephalin (middle), and dyn (right) on potentials in the D-PAG evoked by acupoint stimulation. Top Control, middle 10 min post application of the antisera of opioids, and bottom recovery 20 min afterward

## 2.6

**Activation of the Spinal Acupuncture Analgesia Afferent Pathway by Morphine [8, 11, 12, 14, 18]**

Potentials evoked in the D-PAG by stimulation of acupoints are blocked by contralateral lesions of the anterolateral tract or by intrathecal administration of the antiserum to methionine (met)-enkephalin. These potentials are also blocked by naloxone but not by the administration of antisera to leucine-enkephalin or dynorphin [18] (Fig. 12), supporting the involvement of a met-enkephalin pathway activated by morphine. In AA responder animals, dose-response curves of analgesia were obtained for both low and high doses of morphine administered either intraperitoneally or intrathecally. However, in nonresponding animals, only a single dose-response curve for higher doses of morphine was obtained. In AA responders, bilateral lesions of the anterolateral tract or lesions of the D-PAG that is part of the AA afferent pathway abolished dose-dependent responses to low doses of morphine without affecting the dose response to high doses of morphine. Therefore, morphine analgesia produced by lower doses is probably induced by activation of the AA afferent pathway through met-enkephalin receptors in the spinal cord [18]. Such receptors in the spinal AA afferent pathway are likely to be those activated by intraperitoneal morphine at 0.5 mg/kg or intrathecal morphine at 0.05  $\mu$ g/rat that produce morphine analgesia to a degree similar to that of AA [8, 11] (Fig. 13). This mechanism may explain the reason for the similarity between AA and morphine analgesia.

**Fig. 13.** Morphine analgesia mediated by acupuncture analgesia-producing system



## 2.7

**Individual Variations in Effectiveness of AA and Morphine Analgesia [21, 27]**

After treatment with D-phenylalanine (DPA), an inhibitor of enzymes such as aminopeptidase and carboxypeptidase that degrade met-enkephalin, the strong correlation of individual variations in effectiveness between AA and morphine analgesia disappeared. In other words, AA and morphine analgesia were obtained at similar magnitudes in both responders and nonresponders after treatment with DPA.

Individual variation in amplitude of evoked potentials in the D-PAG also disappeared after treatment with DPA [27]. Hence, individual variations in effectiveness of both AA and morphine analgesia might be attributed to the activity of enzymes degrading met-enkephalin in the spinal cord. Higher enzyme activity might reduce met-enkephalin levels and block responses to AA, whereas lower activity might increase met-enkephalin levels, activate AA afferent pathways, and facilitate responses to AA.

## 2.8

**Analgesia Produced by Stimulation of Nonacupoints After Lesioning of the Analgesia Inhibitory System [11, 15, 17, 26, 28]**

As stated previously, potentials in the L-PAG evoked by stimulation of either acupoints or nonacupoints are self-inhibiting. However, after lesions are made in the lateral centromedian nucleus of the thalamus (L-CM) or parts of the posterior hypothalamus (I-PH), evoked potentials in the L-PAG are not self-inhibited and such stimulation results in pronounced analgesia. Analgesia produced by stimulation of nonacupoints after lesioning of these areas is referred to as nonacupuncture stimulation-produced analgesia (Fig. 11).

Since analgesia from stimulation of nonacupoints is induced by stimulation of acupoints only after lesions occur in the I-PH or the L-CM, these regions are considered part of an analgesia inhibitory system (AIS) for this type of analgesia (Figs. 1, 11). Thus, the AIS may have an important role in distinguishing between acupoints and nonacupoints, since it inhibits afferent impulses arising from stimulation of nonacupoints but not those arising from stimulation of acupoints.

## 2.9

**Afferent and Efferent Pathways That Produce Nonacupuncture Stimulation-Produced Analgesia [26]**

Nonacupuncture stimulation-produced analgesia (non-AA) can be blocked by hypophysectomy and lesions of the non-AA afferent pathway. This system is inhibited dose-dependently by dexamethasone but not by naloxone; unlike AA, non-AA does not exhibit individual variations in effectiveness [26]. Potentials in the L-PAG evoked by stimulation of nonacupoints are not abolished by intrathecal administration of antisera to met-enkephalin or leu-enkephalin but are abolished by antiserum to dynorphin (Figs. 1, 12). Hence, dynorphin is believed to be the transmitter of the spinal non-AA afferent pathway [18]. Since dynorphin is not degraded by aminopeptidase or carboxypeptidase, individual variations in effectiveness are not observed in

non-AA. Descending pain inhibitory systems such as those found in the acupuncture efferent pathway are common in non-AA and AA. The afferent pathway for this system originates at nonacupoints and ends in the anterior part of the hypothalamic arcuate nucleus (A-HARN) connected to the initial region of the efferent pathway. Lesioning of the AIS augments AA produced by stimulation of acupoints; hence, the acupoint also sends fibers to the non-AA afferent pathway. The augmented component of analgesia is largely antagonized by dexamethasone, and the remainder is antagonized by naloxone [17].

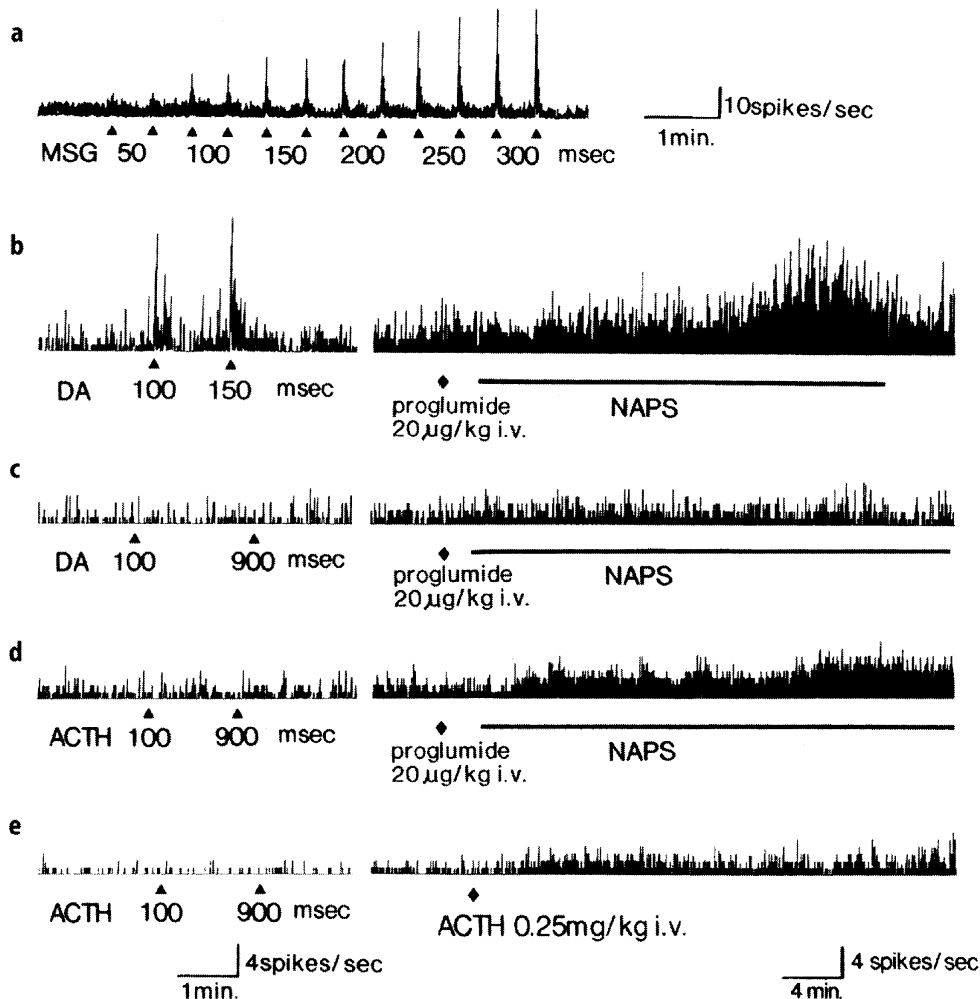


Fig. 14. a 0.1 mM monosodium glutamate (MSG) increased firing rate of P-HARN neuron as application time increased from 50 ms to 300 ms. b Firing rate of MSG-responsive neuron was increased by dopamine applied for 100 and 150 ms. This neuron also responded to nonacupoint stimulation (NAPS) after application of proglumide. c Another MSG-responsive neuron did not respond to 100 ms or 900 ms applications of dopamine. This neuron also did not respond to NAPS after application of intravenous 20 mg/kg proglumide. d Microapplication of same dose of ACTH by picospritzer for 100 and 900 ms produced no change (left) in NAPS-responsive neurons in the P-HARN after intravenous 20 mg/kg proglumide (right). e Microapplication of ACTH into the P-HARN for 100 or 900 ms produced no change in P-HARN neuron activity (left), but intravenous 0.25 mg/kg ACTH increased firing rate of this P-HARN neuron (right)

Lesions of the non-AA afferent pathway block non-AA, and stimulation of the non-AA afferent pathway produces analgesia that is largely reversible with dexamethasone. These lesions are almost completely reversible with dexamethasone plus naloxone (Fig. 11). Transmission between the A-HARN and P-HARN has been found to be dopaminergic, as is that between the M-HARN and P-HARN. Evidence supporting this conclusion is that (1) microinjection of dopamine into the P-HARN produces analgesia dose-dependently and administration of haloperidol antagonizes non-AA dose-dependently, and (2) some neurons in the P-HARN that respond to nonacupoint stimulation when the AIS is inhibited with proglumide also respond to iontophoretically administered dopamine [26] (Fig. 14).

In contrast, other neurons do not respond after either procedure. The afferent pathway of non-AA from nonacupoints divides into two pathways at the L-PAG: one pathway ascends to the A-HARN and the other ascends to the pituitary gland via the median eminence. Lesions of the latter pathway abolish non-AA, but stimulation of this pathway does not in itself produce analgesia [28] (Figs. 1, 5).

## 2.10

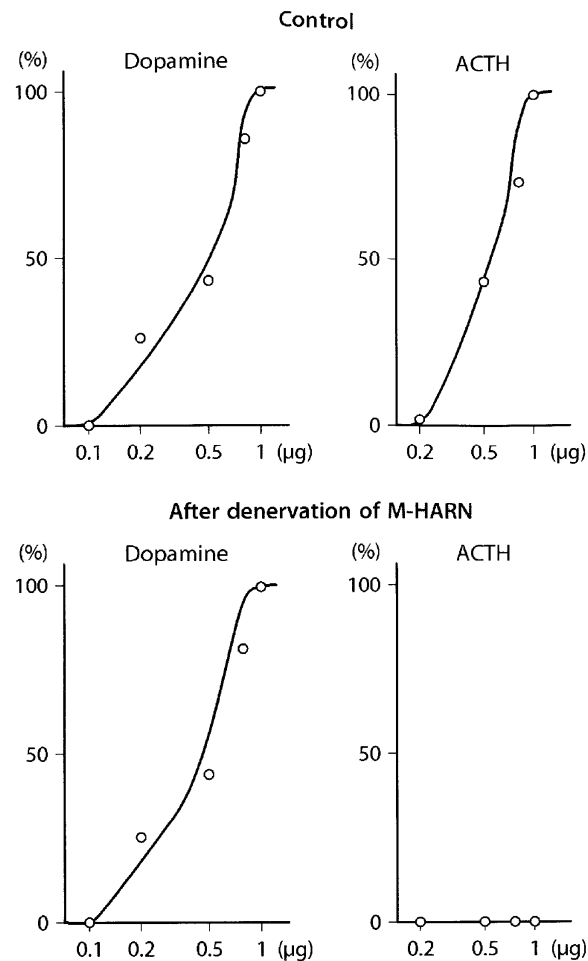
### Pituitary Hormones and Nonacupuncture Stimulation-Produced Analgesia

Adrenocorticotrophic hormone (ACTH) released from the pituitary gland seems to be essential for dopaminergic transmission between the A-HARN and P-HARN. This follows, since dexamethasone microinjected into the P-HARN antagonizes non-AA dose-dependently, while ACTH administration mimics non-AA dose-dependently [26]. Therefore, two neurotransmitters are necessary for transmission between the non-AA afferent and efferent pathways in the arcuate nucleus. Dopamine has been found to act postsynaptically, while ACTH acts presynaptically at this synapse. Evidence in support of these conclusions is that after denervation of the A-HARN, analgesia produced by ACTH microinjected into the P-HARN disappears but that produced by dopamine microinjected into the P-HARN is unaffected [26] (Fig. 15).

Furthermore, neuronal activities that occur in response to stimulation of nonacupoints during administration of proglumide do not respond to iontophoretically administered ACTH [26] (Fig. 14). Beta-endorphin and ACTH released concomitantly from the pituitary gland might be the presynaptically acting neurohumoral factors in AA and non-AA, producing dopaminergic transmission in the P-HARN (Fig. 5). The possibility that ACTH acts as a neurohumoral factor in other regions of the non-AA afferent pathway has been examined by recording potentials evoked by nonacupoint stimulation after lesioning in the A-HARN, the final station of the non-AA afferent pathway. Such evoked-potentials in the A-HARN are enhanced by intraperitoneal administration of ACTH and are markedly decreased by hypophysectomy. However, these decreased potentials are restored by intraperitoneal administration of ACTH. Consequently, ACTH might act on the afferent pathway of non-AA before entering the A-HARN [22] (Fig. 16).

Microinjection of ACTH onto sites of the non-AA afferent pathway such as the L-PAG and the anterior hypothalamus produces dose-dependent analgesia. Conversely, microinjection of dexamethasone antagonizes analgesia dose-dependently [23] (Fig. 17). Furthermore, intraperitoneal ACTH produces dose-dependent analgesia, intraperitoneal dexamethasone blocks non-AA dose-dependently, and intravenous

Fig. 15. Control. Dose-response relationships for dopamine and ACTH microinjected into the P-HARN and analgesia produced. Analgesia due to ACTH disappeared after denervation of the A-HARN while that of dopamine remained unchanged



ACTH stimulates neuronal activity in some P-HARN neurons [26]. These findings suggest that ACTH acts as a synaptic neurotransmitter and dexamethasone acts as an antagonist at these sites.

## 2.11

### Sites of Inhibition from the AIS in the Non-AA Afferent Pathway [15, 17]

Inhibition of evoked potentials and neuronal activity in the L-PAG induced by nonacupoint stimulation is observed in rostral but not caudal regions of the L-PAG. Similarly, stimulation of the I-PH or the L-CM completely inhibits nonacupoint-evoked potentials in rostral but not caudal L-PAG [17]. Therefore, the AIS exerts its inhibitory effects in the region between the rostral and caudal L-PAG in the non-AA afferent pathway. Inhibition of potentials in the rostral L-PAG evoked by nonacupoint stimulation during stimulation of the I-PH is abolished by lesions of the L-CM; hence, nonacupoint stimulation activates the I-PH first and then the L-CM [17].

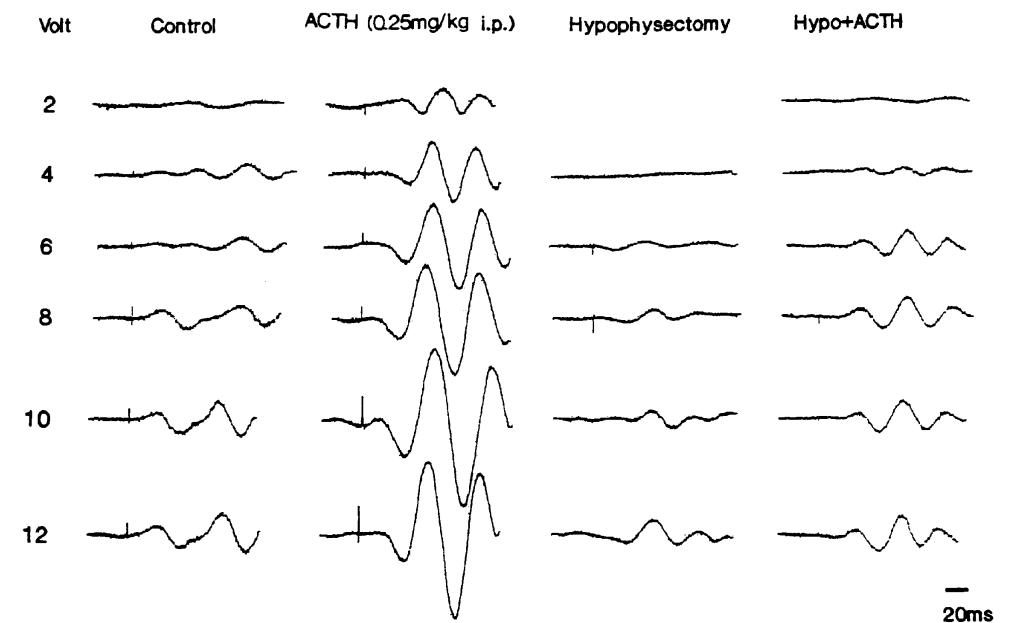


Fig. 16. Effect of 0.25 mg/kg ACTH before and after hypophysectomy on potentials in the A-HARN evoked by NAP stimulation in L-CM-lesioned rats. *Column 1* Control potentials were increased with increasing stimulus strength in volts (V, 0.05 ms duration) indicated by numbers at left. *Column 2* Potentials 30 min after application of ACTH. *Column 3* Effect of hypophysectomy on potentials. *Column 4* Effect of 0.25 mg/kg ACTH (IP) on potentials after hypophysectomy

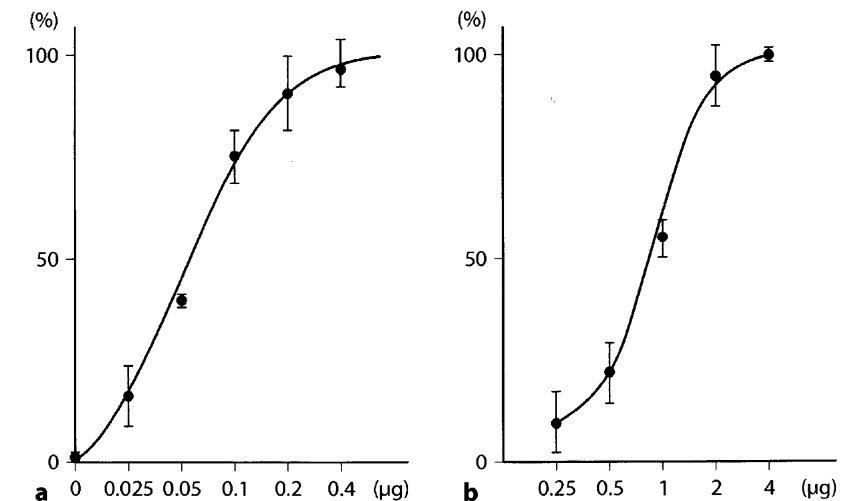


Fig. 17. *a* Dose response of antagonism by dexamethasone microinjected into the L-PAG. *b* Dose response of analgesia produced by ACTH microinjected into the L-PAG. Ordinate numbers: antagonism (A) and analgesia (B) in percent. Abscissas doses of dexamethasone (A) and ACTH (B)

## 2.12

## Neurotransmitters in the Analgesia Inhibitory System and Nonacupuncture Stimulation-Produced Analgesia

Non-AA of the AIS is produced by stimulation of nonacupoints after intraperitoneal treatment with DPA or proglumide, an antagonist of cholecystinin (CCK), rather than after lesions of the L-CM or I-PH [20]. Activation of the AIS by stimulation of nonacupoints is obvious during spontaneous neuronal activity of the L-CM, which increases markedly 10 minutes after the onset of nonacupoint stimulation. Such enhancement of neuronal activity is blocked by treatment with proglumide, suggesting that CCK is a neurotransmitter in the AIS [2].

The timing of the onset of enhancement of neuronal activity in the L-CM (Fig. 18) corresponds fairly well with the timing of the onset of self-inhibition of evoked potentials in the L-PAG after the onset of nonacupoint stimulation [14] (Fig. 10). This finding is supported by the increase in CCK-like immunoreactivity in perfusate collected from the L-CM with the push-pull method. Stimulation both of acupoints and nonacupoints significantly increased CCK-like immunoreactivity in the L-CM but produced no increase in the cerebral cortex [31] (Fig. 19). After microinjection of proglumide or DPA into the I-PH or L-CM, analgesia is produced by stimulation of nonacupoints. Of several CCK antagonists microinjected into the L-CM, L365,250 was the most effective in producing non-AA. These results further support the suggestion that CCK-8 is a principal neurotransmitter in the L-CM [2].

## 2.13

## Effects of Adrenalectomy on AA and Non-AA [7]

Acupuncture analgesia and non-AA are abolished 12 and 24 hours after adrenalectomy, respectively. However, both are restored 1 hour after IV or IP administration of 1–2 ml of 5% NaCl. Sodium ions are required for the action of met-enkephalin and dynorphin in both the AA and non-AA afferent pathways in the spinal cord. Sodium

Fig. 18. Changes of L-CM neuronal activity during nonacupuncture point stimulation and antagonistic action of proglumide. Neuronal activity (A) during nonacupuncture point stimulation. Ordinate numbers integrated spikes/2 s. Abscissa time in minutes. Time scale 4 min. Effect of IV 20 mg/kg proglumide on neuronal activity changes. Effect of 20 mg/kg proglumide 6 min prior to onset of nonacupuncture point stimulation on the L-CM neuronal activity. Arrow indicates application of proglumide. Solid lines under records indicate nonacupuncture point stimulation (NAPS)

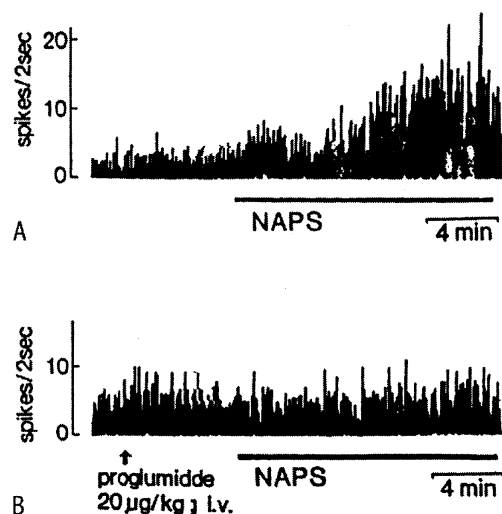
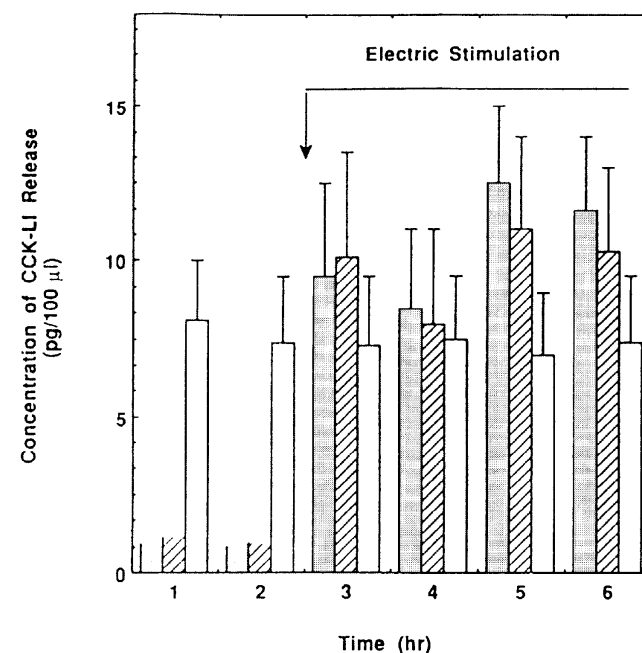


Fig. 19. Effect of 1 Hz peripheral stimulation on release of CCK-like immunoreactivity (CCK-LI) from medial thalamic and cerebral cortex. Dotted Column from thalamus by stimulation of Zusanli, Hatched column from thalamus by stimulation of abdominal muscle, Open column from cortex by stimulation of abdominal muscle. The concentration of CCK-LI in thalamic dialysate before stimulation was lower than the detection limit (5 pg/100 µl)



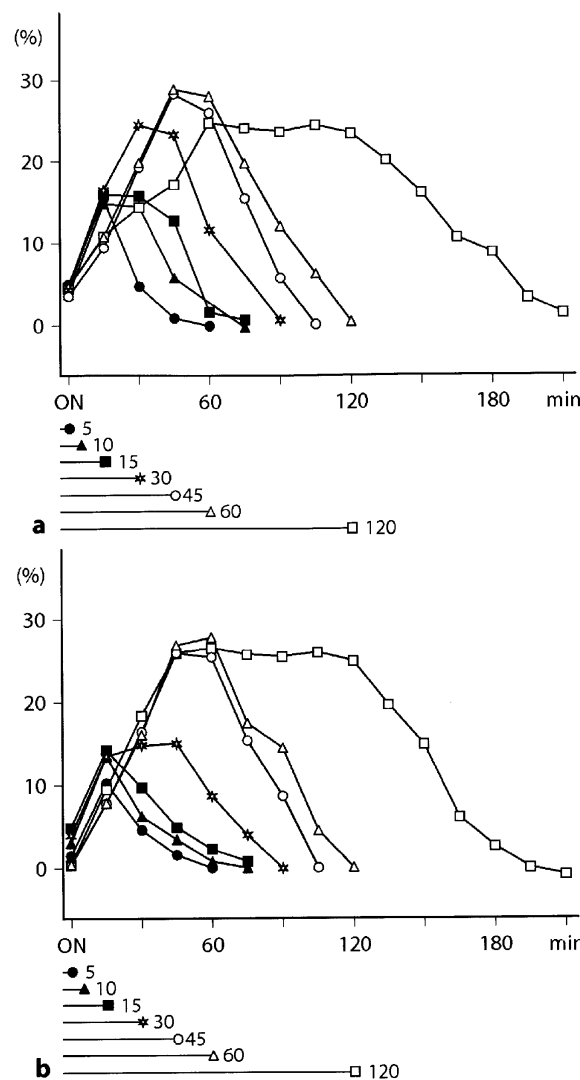
is also needed for the presynaptic actions of  $\beta$ -endorphin and ACTH in the P-HARN. These conclusions are supported by the abolition of acupoint- or nonacupoint-evoked potentials in either D-PAG or L-PAG, respectively. They are also supported by the analgesia produced following microinjection of  $\beta$ -endorphin or ACTH into the P-HARN after adrenalectomy and by their recovery after application of sodium chloride. Therefore, the adrenal gland plays a prominent role in production of both AA and non-AA by maintaining sodium levels in the blood independently of the action of the pituitary gland.

## 2.14

## Aftereffects of AA and Non-AA [30]

Acupuncture analgesia characteristically persists long after termination of acupuncture stimulation. This aftereffect becomes dominant 60 min after stimulation and is still marked at 120 min post stimulation at 1 Hz. The same pattern is observed with non-AA [2] (Fig. 20). The presence of long-lasting effects in both AA and non-AA suggests that an analgesic mechanism is activated without afferent impulses produced by stimulation of acupoints and nonacupoints. As stated earlier, hypophysectomy abolishes both AA and non-AA, and this procedure abolishes potentials in the M-HARN and A-HARN evoked by stimulation of the acupoints and nonacupoints, respectively. However, abolished potentials in these final regions of the AA and non-AA afferent pathways are temporarily restored by intravenously administered morphine and ACTH, respectively. This finding implies that an increased amount of  $\beta$ -endorphin and ACTH results in a longer period of analgesia. Acupoint or nonacupoint stimulation restores the transmission in the regions of the AA and non-AA afferent pathways.

**Fig. 20. a** Changes of acupuncture point stimulation-produced analgesia as related to stimulation period ( $n = 6$ ). **b** Changes of nonacupuncture point stimulation-produced analgesia as related to stimulation period ( $n = 6$ ). Ordinate numbers percent increase of tail flick latency, Abscissa time in minutes, Bars under figure indicate stimulation period



During electroacupuncture, major increases of  $\beta$ -endorphin and ACTH have been detected in peripheral blood [5]. Both peptides show a continual increase up to 80 minutes after termination of acupuncture stimulation. Furthermore, an analgesic effect was induced in cross-circulation recipient rats after electroacupuncture was applied to donor rats [4]. An increase of endorphins in the cerebrospinal fluid after electroacupuncture [9] suggests a correlation between cerebral and peripheral  $\beta$ -endorphin levels [5]. The characteristic, frequency-analyzed EEG changes in the deep structure of the brain induced by acupoint stimulation of donor rabbits also appears in cross-circulation recipient rabbits [29]. Since met-enkephalin is a putative neurotransmitter in the AA afferent pathway of the spinal cord, ACTH may be the transmitter in the L-PAG and the anterior hypothalamus in the non-AA afferent pathway. Beta-endorphin and ACTH, coreleased from the pituitary gland, are likely to reach levels high enough to activate these regions. Extended periods of stimulation might

also activate the AA and non-AA afferent pathways in which excitability may increase due to post-tetanic potentiation without ongoing afferent impulses.

## 2.15

### Conclusions

Acupuncture analgesia is produced by activation of the DPIS through a specific pathway connected to the acupoints while still allowing maintenance of consciousness. In contrast, the AIS is activated by stimulation of acupoints or nonacupoints, leading to nonspecific inhibition of different interconnected pathways. Therefore, acupoints and nonacupoints can be distinguished by their anatomically distinct brain pathways. The aftereffects of AA might be produced by the actions of an increased amount of  $\beta$ -endorphin released from the pituitary gland on components of the AA-producing pathway.

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## Opioid and Antioioid Peptides: A Model of Yin-Yang Balance in Acupuncture Mechanisms of Pain Modulation

J.-S. Han

### 3.1

#### Introduction

At first glance, sharp differences exist between medicinal practices originating in the east and in the west. While Western medicine is more technological, relies on quantitative measurements, and is increasingly evidence-based, Eastern medicine is minimally invasive, relies on qualitative assessments, and remains largely experience-based. However, one concept shared by both medical systems is that most if not all physiological functions are regulated by activities possessing opposite effects. To consider only a few examples, blood sugar is decreased by insulin and increased by glucagon, calcitonin and parathyroid hormone act in opposing directions to regulate calcium levels in blood and tissues, and, generally speaking, the sympathetic and parasympathetic systems have contrasting functions in regulating many aspects of our internal environment. These phenomena can be regarded as reflections of the yin-yang balance described in traditional Chinese medicine. Thus, the "homeostasis" of Western medicine has long been recognized as "dynamic balance" in the classical texts of Chinese medicine.

The discovery of enkephalins, the first family of endogenous opioids, by Hughes et al. in 1975 [1] triggered the search for endogenous substrates with antioioid activities. Ungar et al. [2] were among the first to present evidence for antioioid substances [AOS]. At present, an array of AOS has been reported, the most widely studied and probably the most potent of which is cholecystokinin octapeptide (CCK-8) [3].

Studies of the interactions between opioid peptides and antioioid peptides are of considerable pharmacological and physiological interest, especially when the ever-increasing functions of endogenously released peptides are considered. As with all peptides, the endogenous opioids and antioioids have been best studied in animal models. Using such models, acupuncture (manipulation of metal needles inserted in specific body sites known as acupoints) and electroacupuncture, or EA (electrical stimulation administered via the needles placed at acupoints), have been shown to be reliable approaches for inducing release of endogenous opioid peptides in the CNS [4]. More recently, animal studies have also demonstrated the acupuncture-induced release of antioioid substances and examined the functional interactions between these opposing classes of peptides in producing acupuncture analgesia (AA). The aims of the present chapter are to review (a) the current understanding of the involvement of endogenous opioid peptides in AA, (b) the role of CCK in determining the

