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NEUROCHEMICAL BASIS OF ACUPUNCTURE ANALGESIA

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A review on acupuncture and its neurochemical basis may not seem to be within the general scope of this series. However, the phenomenon has attracted the interest of scientists from several disciplines, including pharmacologists, and the use of drugs as probes has been instrumental in establishing the neurochemical basis of acupuncture.

We have found it necessary to limit our review to studies of acupuncture for the relief of pain since research in other areas is still in its infancy. Since much of the work in this field has been published in periodicals not easily accessible to the general scientific community for linguistic or other reasons, we have chosen to provide a fairly extensive documentation.

Although acupuncture has a very long history as a means for relieving pain (1, 2), its scientific study began very recently. Early studies revealed that the analgesic effect was blocked by procaine infiltration of acupuncture points and that it was not possible to induce analgesia in paraplegic or hemiplegic patients, pointing to the importance of afferent transmission (3–6). Involvement of chemical mediators in the central nervous system (CNS) was suggested from experiments where the cerebrospinal fluid (CSF) of donor rabbits given acupuncture was infused into the cerebral ventricles of recipient rabbits, increasing their pain thresholds (7).

An important series of findings came in the 1970s when several investigators presented carefully controlled experimental studies using different approaches. Andersson et al verified the effect of acupuncture on thresholds to pain, experimentally induced by tooth pulp stimulation in healthy volun-

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teers (8). Applying the signal detection theory, Chapman and co-workers proved the existence of a biological component for acupuncture as well as a central biasing effect (9). However, the most exciting finding was the report by Mayer and associates that the analgesic effect of acupuncture on electrically induced tooth pulp pain in man could be partly reversed by naloxone, a specific opiate antagonist, indicating the participation of endogenous opioids in acupuncture analgesia (10, 11). Their results were soon confirmed in studies in healthy volunteers (12), in patients with chronic pain (13), and in a variety of laboratory animals (14–18).

The recent scientific interest in acupuncture and its mechanisms shows a timewise coincidence with the discovery of the endogenous opioids, the endorphins. It has been commonplace to assume that acupuncture acts via release of these substances and research along this line has provided ample evidence for the existence of such a connection. However, it has also become clear that other neuronal systems are involved. This is not unexpected in view of the complex and integrated nature of the nervous system. It may therefore be more appropriate to discuss pathways and circuits activated by acupuncture rather than single systems.

It must be stressed that the term acupuncture is used for a number of related, but in terms of mode of action not necessarily identical, techniques. It is therefore essential to define the stimulus procedure, being mechanical (manipulation of needles) or electrical via stimulation of needles (electroacupuncture, EA), or via surface electrodes (transcutaneous nerve stimulation, TNS). The stimulus parameters may vary considerably according to the intensity, duration, and frequency. The frequency can be low (less than 10 Hz) or high (100 Hz or more) and the intensity can be weak just to activate Aβ fibers or high enough to activate Aδ or even C-fibers. Differences in stimulation characteristics lead to differences in the induced effects, probably also in terms of mechanisms of action. It is commonly claimed that only low-frequency stimulation paradigms which cause muscle contraction mimic acupuncture in giving generalized analgesia with prolonged induction latency and after-effect [(4, 7–9, 13, 17, 19); B. Kaada, personal communication]. On the other hand, high frequency stimulation of lower intensity (so-called conventional TNS) causes local or segmental analgesia and may therefore activate other afferent pathways and CNS systems and consequently bear little resemblance to acupuncture (17, 19, 20). In this review, the term acupuncture will be used in a general sense to indicate classical acupuncture or low frequency, high intensity electrical stimulation and will be further specified with regard to the stimulus characteristics. More details on neurophysiologic aspects of acupuncture are summarized elsewhere (21).

Another point raising considerable difficulty is the comparison of acupuncture effects across species, and particularly comparing reactions in lower species such as rats or rabbits with those in man. It is well-known that in these lower species, analgesia may be induced as a response to stress (immobilization, cold, white noise, etc) and it is not unlikely that acupuncture stimulation may be partly mediated via the stress response. In the clinical use in humans, we will probably also have to consider the involvement of placebo effects, a possibility which is difficult to examine since, for instance, a double-blind study would be impossible to carry out. Another critical consideration in the study of acupuncture is what measures are being used to define the "pain threshold." Clearly, the verbal report in man with tooth pulp stimulation by thermal stimuli involves more integrated pathways than those studied with responses such as the spinal reflexes in rats. A further complexity in the study of these techniques is the interindividual variation in the response. This is sometimes taken advantage of when establishing the mechanisms of action; responders are then compared with nonresponders with regard to neurochemical or other variables.

5-HYDROXYTRYPTAMINE (5-HT)

The physiological and pharmacological implications of 5-HT in pain and analgesia, especially in relation to morphine action, has recently been summarized (22). Evidence presented below indicates an equally important, if not the prevalent role for central 5-HT in mediating acupuncture analgesia. The descending 5-HT fibers from the raphe magnus nucleus have been regarded by most authors to be particularly significant in this respect, as suggested by Kaada (22a).

The Effect of Changing the Functional Activity of Central 5-HT on Acupuncture Analgesia

Lesions at the raphe level will among other things interfere with the 5-HT system. Lesioning of the dorsal raphe nuclei (23) and the dorsal and medial raphe nuclei (24) interferes with the effect of electro-acupuncture (EA). The effect is manifest within 7 to 9 days (23) or 2 to 7 days with reversal after 14 days (24). It seems quite general since it is independent of EA being applied to the back (23) or the lips (24) of the animal. The inhibitory effect of acupuncture on viscero-somatic discharges in intercostal nerve induced by splanchnic nerve stimulation will disappear completely after lesioning of the medial portion of the medulla oblongata while it remains intact in decerebrated preparations (25). The effect of acupuncture on the potentials evoked in the orbital cortex of the cat by splanchnic nerve stimulation is

also markedly attenuated after lesioning of the raphe magnus nucleus or the dorsolateral funiculus (26). A decrease of acupuncture analgesia was also observed in a series of experiments after electrolytic lesioning of the raphe magnus nucleus (27, 28) or after the selective chemical lesioning with 5,6-dihydroxytryptamine (29) in rats (30), cats (31) or rabbits (32), a procedure known to cause degeneration of the descending 5-HT fibers (33). However, the reduction in acupuncture analgesia was usually transient and disappeared 3 days after the treatment (27, 30, 31), indicating the possible existence of compensatory mechanisms.

The importance of descending 5-HT pathways seems well supported. Recently, data have appeared indicating the importance also of ascending 5-HT fibers in the mediation of acupuncture analgesia. Thus, bilateral microinjection of 5,6-dihydroxytryptamine into the medial forebrain bundles of the rat brain causes a selective decrease of the cerebral 5-HT content and a concomitant lowering of the effect of acupuncture as measured by tail flick latencies (34).

Pharmacologic manipulation of the 5-HT functional state has been studied extensively, particularly by Chinese investigators. The blockade of 5-HT biosynthesis generally reduces acupuncture analgesia. The administration of *p*-chlorophenylalanine (pCPA), a 5-HT synthesis inhibitor, into the lateral ventricles of the rabbit in a paradigm which reduces 5-HT in the diencephalon, inhibits acupuncture analgesia (35). Similar results have been reported with intraperitoneal injection (32). In rats injected with different doses of pCPA (36) or in groups of rats killed on different days after a maximum dose of pCPA had been given (37, 38) there was a parallel lowering of cerebral 5-HT content and attenuation of acupuncture analgesia. *p*-Chloroamphetamine was found to be more potent than pCPA in this respect (39). Woolf et al found that pCPA was effective in blocking the antinociceptive effect of segmental electric stimulation in intact but not in spinal rats, implying that the antinociceptive effect in the intact animal was mediated partially by the descending 5-HT fibers from the suprasegmental structures (40). A conflicting report announcing that the analgesic effect elicited by electric stimulation of the tail of the rat is enhanced rather than attenuated by pCPA treatment (41) requires confirmation.

The blockade of 5-HT receptors by cyproheptadine significantly reduced acupuncture analgesia in rabbits (32) and similarly, another 5-HT receptor blocker, cinanserine, was reported to abolish the effect of acupuncture analgesia in the rat (39). To characterize the sites of action more precisely, cinanserine was microinjected into various brain nuclei of the rabbit. Significant attenuation of acupuncture analgesia was noticed in the amygdala, nucleus accumbens, habenula, periaqueductal gray, and the spinal cord, suggesting multiple sites of action at different levels (J.S. Han et al, in

preparation). The effect of D-lysergic acid diethylamide (LSD) has been found to be biphasic: augmentation of analgesia at small doses (42, 43) and slight antagonism at large doses (43). These findings are compatible with the dose-dependent, complex modes of action of this agent (44).

Several studies indicate that 5-HT precursor loading affects acupuncture analgesia. A definite potentiation was reached with a dose of 60–80 mg/kg 5-hydroxytryptophan (5-HTP) which increased the cerebral 5-HT content by more than 100% (34). Compared with the conspicuous augmentation of acupuncture by 5-HT (34, 37, 39), a marginal (39) or insignificant (34) increase was obtained with systemic administration of tryptophan which, however, resulted in an increase of cerebral 5-HT by only 30% (34).

Blockade of 5-HT degradation with pargyline, a monoamine oxidase inhibitor, induces a marked potentiation of the effect of acupuncture (45), an effect which cannot be antagonized by the opiate antagonist naloxone (16). The effect vanished with time, probably owing to the general elevation of the cerebral content of catecholamines (46), which seem to reduce the effectiveness of acupuncture. Clomipramine, which blocks 5-HT re-uptake with little effect on catecholamine systems, was used in a double-blind clinical trial involving the removal of the third impacted molar under "finger-pressing anesthesia." Ninety minutes prior to the operation, consecutive patients were given one of the following treatments: (*a*) 50 mg clomipramine, (*b*) 50 mg pargyline, or (*c*) placebo. The analgesic effect was much better in the clomipramine group ($n = 36$) than in the placebo group ($n = 36$), while a slight, nonsignificant augmentation of analgesia was observed in the pargyline group ($n = 18$) (47).

As evidenced above, activation of the central 5-HT system potentiates the effect of acupuncture analgesia. This suggests a pivotal role of central 5-HT in these mechanisms. However, since it has also been found that the impairment of acupuncture analgesia following the destruction of 5-HT pathways usually is partial and transient, other neuronal substrates may assume the role of 5-HT.

Changes in the Turnover Rate of Central 5-HT During Acupuncture Analgesia

An increase of the cerebral content of 5-HT and its metabolic product 5-hydroxyindoleacetic acid was found in rabbits (48–50) and rats (34, 39, 51) under EA for 15–60 minutes. The most prominent and consistent changes took place in the lower brain stem (34, 48, 50, 51), especially in the raphe area (50, 51), and in the spinal cord (34). An interesting notion was that the increase of central 5-HT could be detected only in those rats with prominent analgesic effect (the EA responders), while no significant change was noticed in the nonresponders under the same conditions of EA (52).

In this study, a correlation between increases in brain 5-HT content and increases in tail flick latencies was observed. It was also found that a prolongation of the EA stimulation period caused corresponding increases in cerebral 5-HT content as well as in the pain thresholds (52).

Evidence for the involvement of 5-HT in acupuncture analgesia also derives from studies of its turnover using pargyline and probenecid. EA seems to accelerate the rates of synthesis and utilization of 5-HT in the brain and spinal cord (34). The rate of synthesis prevails over that of utilization, which provides a plausible explanation for the increase of the steady-state concentration in the CNS. Indirect observations suggest an effect of acupuncture on 5-HT release (53). Here, tritium-labeled 5-HT was given intraventricularly and classic acupuncture on hind leg points evoked the release of tritium into ventriculo-cisternal perfusate.

In summary, a key role of 5-HT in acupuncture analgesia has been established. Two distinct central 5-HT pathways seem to be involved. A descending pathway emanating from the raphe magnus nucleus and inhibiting nociceptive transmission at the spinal level has been well-documented (25, 26, 54, 55). This system is also activated by intracerebral stimulation analgesia (56). Ascending pathways originating from the midbrain raphe are also activated (57), causing the release of 5-HT in the forebrain structures (53, 58). The role of this system in acupuncture analgesia is not yet fully understood.

ENDOGENOUS OPIOID SUBSTANCES (ENDORPHINS)

Essentially two approaches have been taken to establish the role of endorphins in acupuncture analgesia. The principal pharmacological approach has usually been to use naloxone, under the assumption that it is a specific antagonist for opioid receptors mediating analgesia. Although this assumption is generally held to be valid (59), recent work indicates that opioid receptors are heterogenous with some subpopulations having comparatively low affinity for naloxone (60). The dose of naloxone may therefore become critical. The other principal approach to study endorphin mediation of acupuncture analgesia is the direct measurement in brain, CSF, or other fluids. Here one is faced with methodological problems in terms of specificity, relating to the multiplicity of the endorphin systems and to the low circulating levels and high potency of these peptides (61). Also, the significance of altered tissue levels in terms of changes in neuronal dynamics is unclear.

Reports that acupuncture analgesia can be temporarily and at least partly blocked by naloxone are abundant. The studies have involved a variety of

species and experimental designs. In man, pain has been induced experimentally by electric stimulation of the tooth pulp (11), electric or thermal stimulation of the skin (12), or by hypertonic saline injected into the intravertebral ligaments (62). In each study, the pain-relieving action of acupuncture was reversed by naloxone. Intravenous doses of 0.4–0.8 mg of naloxone reversed the analgesic effect elicited by acupuncture-like TNS (2 Hz) in six out of ten chronic pain patients, while pain relief induced by conventional TNS (100 Hz) was not affected, even with a dose as high as 1.6 mg (13). Chapman and co-workers seem to have an opposite view, since they found that naloxone partially reversed the analgesic effect of conventional TNS (63), but not that induced by 2 Hz stimulation (64).

Since acupuncture may act as a placebo or by suggestion, the results concerning naloxone reversal of acupuncture analgesia should be considered in this regard. However, hypnotic analgesia is generally not reversed by naloxone (65–67) and placebo analgesia can only be reversed by very high doses of naloxone (7.5–10 mg), but not by doses effective in narcotic overdosing (0.4–2 mg) (68, 69). This suggests a difference in underlying mechanisms between acupuncture analgesia on one hand and the placebo and hypnotic analgesia on the other.

A model of clinical acupuncture has been established in monkeys using operant conditioning responses for assessment (70, 71). EA was applied to the hand points and noxious stimulation to the skin of the forearm ("adjacent segmental") or the leg ("distant segmental"). Low frequency (2 Hz) EA gave better analgesic effect in distant areas with after-effects as long as 30 minutes, while high frequency (80 Hz) gave better results in the local area with short after-effect. Direct electrical stimulation of the homosegmental cutaneous nerve provided the strongest analgesia with little after-effect. Reversal of acupuncture analgesia by 0.05–0.1 mg/kg naloxone was almost complete in 2 Hz low frequency EA, partial in 80 Hz EA, and weak after direct cutaneous electric stimulation, emphasizing the most important role for endorphins is in low frequency EA (70, 71).

Studies have been extended to various nonprimates. In cats, acupuncture analgesia is reversed by naloxone with effective doses of 0.3 mg/kg (72), and 0.02–0.04 mg/kg (73), respectively. In rabbits, systemic naloxone fails to reverse acupuncture analgesia at doses of 0.1 mg/kg (74) or 0.15–0.2 mg/kg (32). However, when given intraventricularly, 40 μg naloxone was sufficient to give partial reversal (16). The conflicting results may depend on differences in acupuncture protocols. Thus, intravenous naloxone at 0.4 mg/kg was reported to reverse "weak" EA but not "strong" EA, the latter considered as equivalent to stress analgesia (75). Experiments with other antagonists have also been reported. Intravenous injection of 3 mg/kg of levallorphan was reported to be effective to reverse analgesia (18). A partial reversal was also reported in experiments using cortical evoked potentials

(76) or viscero-somatic reflexes (77) as the end-points. In a recent report, a complete reversal of acupuncture analgesia was shown 16 hours after the intraventricular injection of naloxazone, an antagonist for high affinity opiate receptors being almost irreversible (78). Pomeranz et al reported that the analgesic effect of EA in mice could be completely reversed by naloxone (14) or other so-called type I opiate receptor antagonists, including naltrexone, cyclazocine, and diprenorphine (79). While naloxone blocked the analgesic effect of 4 Hz EA completely, it had little effect on that of 200 Hz EA (80), a result quite compatible with the experience from primates. In rats, the analgesic effect of EA was shown to be completely blocked by levallorphan (81), or partially reversed by naloxone (82). Woolf and associates found the segmental antinociceptive effect of 100 Hz TNS to be partially blocked by naloxone, both in intact and in spinal rats (40), suggesting that activation of endorphins is one of the mechanisms by which the innocuous input exerts its inhibitory effect on nociceptive reflexes at the segmental level.

Studies with microinjection of naloxone were performed in rabbits and rats to determine the areas where endorphins act as acupuncture mediators. A significant attenuation was observed when naloxone was infused into the periaqueductal gray, habenula, septum, nucleus accumbens, or amygdala, whereas no effect was observed when the same amount of naloxone was injected into the hippocampus, caudate nucleus, thalamic structures near habenula, or into the ventricular system (83). Administration of naloxone into periaqueductal gray of the rabbit not only blocked the analgesic effect elicited by EA on the forelimb points (84), but also blocked the analgesia elicited by electric stimulation of the caudate nucleus (85), suggesting that pathways emanating from the caudate nucleus may release endorphins into the periaqueductal gray. Blockade of acupuncture analgesia was also observed in rats when naloxone was injected into the nucleus accumbens or habenula (86). Another study in rats has indicated a role for endorphin activation at the spinal level as evidenced by intrathecal naloxone administration (C. W. Xie, J. Tang, and J. S. Han, unpublished).

Ehrenpreis and co-workers found that the administration of D-phenylalanine or D-leucine, weak inhibitors of carboxypeptidase A and leucine aminopeptidase, caused an elevation of hot plate latency in mice, an effect which was reversed by a large dose of naloxone (87). Combined use of EA with D-amino acid in mice resulted in a summation effect (88). Small doses of D-phenylalanine given intraventricularly to rabbits in doses as small as 0.2 mg/kg could bring about a marked potentiation of the effect of acupuncture without affecting the basal pain threshold (89). There was also evidence for an increase of cerebral endorphin content after EA stimulation, as well as an enhancement of the effect of acupuncture without effect on the basal tail flick latency (90). Blockade of peptide degradation by bacitracin admin-

istration also increases the cerebral enkephalin content and lengthens the after-effect of acupuncture, which is blocked by a naloxone injection (91). Bacitracin has no effect on the brain level in the quiescent state, indicating that the tonic activity of the enkephalinergic neurons is low and that strong stimulation such as with acupuncture is required for activation. It would be of interest to repeat these studies with a more selective blocker of enkephalin degradation such as thiorphan (92). It has also been found that the intraventricular injection of cycloheximide, an inhibitor of protein synthesis, reduces the increment of cerebral enkephalin content after EA stimulation and attenuates the analgesic effect (91). Further support for the involvement of opiate receptors derives from experiments with opiate receptor deficient (CXBX) mice. Although their basal pain threshold and brain endorphin levels were not significantly different from that of conventional mice (93), the pain threshold increased after D-amino acid administration (94) and the effect of acupuncture was significantly less marked than in control animals (95).

The involvement of the pituitary for acupuncture analgesia is still a matter of debate. The observation that the analgesic effect of EA in mice was abolished after hypophysectomy led Pomeranz and associates to the conclusion that "a morphine-like pituitary peptide mediates acupuncture analgesia" (15). Another piece of evidence in favor of this supposition is the disappearance of analgesia after a transverse section at the midbrain level in the cat (15), although this was not confirmed by others (25). Pituitary suppression in mice by dexamethasone administration or addition of saline to the drinking water attenuates the analgesic response (96). Radioreceptorassay revealed that dexamethasone lowered the pituitary endorphin content, while bilateral adrenalectomy increased both the pituitary endorphin content and the effectiveness of acupuncture (97). EA for 30 minutes in rats causes a decrease in the pituitary endorphin content (98, 99) and concomitant increase in plasma endorphin levels (98), implying release from the pituitary into the blood stream. Release of naloxone reversible analgesic activity has also been reported to appear in the blood of the rabbit (100, 101) or cat (102) following EA stimulation. However, even if there is convincing evidence for pituitary release of endorphins during acupuncture, this release may not be causally related to the analgesic effect, since entrance of opioid peptides into the CNS is very limited (103). Very high plasma concentrations of β-endorphin (104) or enkephalin (105) are needed to produce analgesic effects and these concentrations are not met under physiological situations. The possibility of direct transfer of pituitary hormones to the brain via retrograde blood flow (106) should, of course, not be neglected. Another point worthy of consideration is that pituitary mechanisms not involving endorphins seem to be important in stress-induced analgesia (108, 109).

Changes in the Content and Release of Endorphins During Acupuncture Analgesia

As already pointed out, interpretation of changes in tissue endorphin content is not easy, since it is a function of synthesis, storage, release, and metabolism. It can be assumed that levels in brain perfusates or CSF levels will give more reliable information on the dynamic activity in endorphin systems.

EA, alternating at 2–15 Hz for 30 minutes to bilateral hindleg points in rats, has been reported to raise brain endorphin content as assayed in a radioreceptorassay. There was a proportionate increase of tail flick latencies (99). Similar results were obtained by Murai et al, who found the cerebral endorphin content of acupuncture responding rats to be significantly higher than that of the nonresponders (110). In the rat, about 10 minutes of EA stimulation will raise cerebral endorphins significantly, and this elevation outlasted the stimulation by 20 minutes (52). Increases in total endorphin content were found in several brain regions. However, a positive correlation between the degree of analgesia induced and endorphin content was observed only in the midbrain and septum-accumbens (111).

Zhou and associates found a significant elevation in Met- and Leu-enkephalin content in hypothalamus and striatum after 20 minutes of manual needling in rabbits or 30 minutes of EA in rats. No significant changes were found in the lower brain stem, thalamus, hippocampus, or cerebral cortex (91). In a recent study, the β-endorphin content of the rat brain was measured by radioimmunoassay immediately after EA stimulation and correlated with the analgesia. Increases of β-endorphin content were observed and were found to relate to the effect of the treatment (112). Increase of receptor-active endorphins (113) or immunoassayable β-endorphin (114) content after EA stimulation was also found in the brain of mice made tolerant to, and dependent on, morphine. This was attributed to be one of the mechanisms for amelioration of withdrawal symptoms in morphine addicts by the use of acupuncture.

Studies have also been directed to cerebrospinal fluid (CSF) or perfusates of brains or selective areas thereof. Sjölund et al found that acupuncture-like TNS (2 Hz, 30 minutes) for treatment of chronic pain in the trunk or lower extremities elicited an increase of the "Fraction I" endorphins in the lumbar CSF as assayed for opiate receptor affinity against tritium-labeled dihydromorphine. The change in level was not seen in trigeminal neuralgia patients (115), who were stimulated over the trigeminal nucleus, implying a segmental action. An increase of Fraction I in the ventricular fluid was also noticed when the patients were given EA (4–5 Hz, 30 minutes) on hand and forearm points (116). The chemical characteristics of this fraction are not yet fully

known, but some of the activity may relate to dynorphin (117). Pan et al found two active peaks in Sephadex G10 eluates tested over the mouse vas deferens. One fraction co-eluted with Leu-enkephalin, the other showed a chromatographic behavior which differed from that of reference peptides. This latter fraction, named "kephinin," lost activity on digestion by chymotrypsin and produced naloxone reversible analgesia in rabbits after intraventricular injection (118, 119). An increase in immunoassayable β-endorphin but not enkephalin level was found in human CSF when EA (2–3 Hz, 30 minutes) was given for treatment of recurrent pain (120), but the CSF changes seemed to bear no relation to the effectiveness of acupuncture for pain relief. The same research group found an increase in CSF enkephalin in heroin addicts with no change in β-endorphin content (121).

In experiments with rabbits, acupuncture of the hind leg point Zusanli raised the enkephalin content in cisternal CSF when bacitracin was infused into the ventricular system to block enzymatic degradation (91). In another report, push-pull perfusion was performed through chronic coaxial cannulae implanted into various rabbit brain areas. An increase in Fraction I levels occurred in the perfusate collected from the periaqueductal gray which correlated with the effectiveness of acupuncture. No comparable correlation was seen in the other areas (122).

A LINK BETWEEN 5-HT AND ENDORPHINS IN ACUPUNCTURE

As evidenced by the previous presentation, both endorphins and 5-HT of the CNS play an important role in acupuncture analgesia. A study of both neurochemical substrates simultaneously would seem worthwhile. In fact it has been reported that EA-induced increases of the tail flick latency in rats bear a positive correlation with both the increase of cerebral 5-HT and endorphin content (123). Furthermore, lowering the cerebral 5-HT content by pCPA or 5,6-dihydroxytryptamine resulted in an increase of the endorphin content (36), while blockade of opiate receptors by naloxone caused accelerated 5-HT turnover (123). This may explain some seemingly paradoxical phenomena:

1. Blockade of opiate receptors by intraventricular injection of 20 μg of naloxone or induction of a moderate decrease (52%) of cerebral 5-HT content by the intraperitoneal injection of 200 mg/kg of pCPA did not significantly impede the effect of acupuncture in rats, whereas the combined use of both maneuvers reduced acupuncture analgesia conspicuously (123).

2. A decrease in 5-HT content in brain does not necessarily result in an attenuation of acupuncture analgesia in rats. This is probably because the

ability to compensate the decrease of 5-HT with an increase of endorphins varies between animal species (36).

3. Intraventricular injection of 50 μg of naloxone to the rabbit reduces the effect of acupuncture by 50%. However, the same amount of naloxone failed to antagonize acupuncture analgesia when pargyline was used to raise the 5-HT level in the brain (16).

4. No reduction in the effect of acupuncture was observed in a series of rabbits moderately tolerant to morphine. However, acupuncture analgesia became less effective after a small dose (1 mg/kg) of *p*-chloroamphetamine, which was without effect in naive animals (18). Thus, accelerated 5-HT turnover seemed to compensate for a decrease in the efficacy of opioid mechanisms.

NOREPINEPHRINE (NE)

A decrease of the norepinephrine (NE) content of the rat brain by EA was first suggested by Zhao et al in 1964 (124), and has then been confirmed (39, 125–127). Turnover studies have shown that the decrease in NE content is apparently due to accelerated utilization rather than retarded biosynthesis (126), a result compatible with electrophysiological observations showing accelerated unit discharge in the locus coeruleus (128) and the A1 nucleus (129) during EA stimulation.

Neuropharmacological manipulations have been adopted to assess the role of central NE in acupuncture. Reduced efficiency is caused by the intraventricular injection of dihydroxyphenylserine, a precursor which can be readily decarboxylated into NE bypassing the dopamine (DA) step (51, 130). A dose-related and time-dependent decrease of the effect of acupuncture accompanies increases of the cerebral NE level (130). Selective lowering of the cerebral NE content by diethyldithiocarbamate, an inhibitor of dopamine-β-hydroxylase, on the contrary, raised the effectiveness of acupuncture significantly (51). The data suggest an antagonistic role for cerebral NE in the mediation of acupuncture and it is therefore surprising that potentiation of acupuncture was noticed when biosynthesis of catecholamines was blocked by α-methyl-*p*-tyrosine, an inhibitor of tyrosine hydroxylase (39, 51, 131). This apparent controversy prompted further analysis of the problem. Han et al found that administration of the α-blocker phentolamine led to a potentiation both in rats and rabbits, while the α-agonist clonidine presented an opposite effect (131). Moreover, the antagonistic effect of dihydroxyphenylserine on acupuncture was shown to be completely reversed by phentolamine, which, in combination with diethyldithiocarbamate to block NE biosynthesis, has been reported to elicit

a very marked potentiation of acupuncture (39). β-Adrenergic receptors seem to play an opposite but probably minor role, since propranolol significantly reduced the effect of acupuncture in rats (130) and perhaps in rabbits (131). In a clinical trial, the effect of acupuncture anesthesia in thyroidectomy was found to be less marked in patients pretreated with propranolol than in patients in the placebo group (132). The complex nature of NE pathways makes studies of mechanisms difficult. The NE containing neurons located in the lower brain stem send their axons upwards along the dorsal or ventral bundle to the forebrain, or terminate locally, or project in a downward direction along the dorsolateral funiculus to the spinal cord (133). Potentiation of acupuncture was observed after electrolytic lesioning of the locus coeruleus and/or the ascending dorsal bundle (134–136) or the chemical denervation of the ascending ventral bundle by 6-hydroxydopamine (131). Electrical stimulation of the locus coeruleus, on the contrary, caused a moderate attenuation (134, 135). Microinjection in rabbits revealed that clonidine significantly attenuated acupuncture analgesia when injected into the habenula, periaqueductal gray, or nucleus accumbens, but not the amygdala, whereas phentolamine effectively potentiated acupuncture when injected into the habenula (137). Thus, the ascending NE pathway may exert a modulatory role on acupuncture via forebrain structures such as the habenula, periaqueductal gray, or nucleus accumbens. Augmentation of acupuncture analgesia 3–24 hours following the injection of NE into the rat hypothalamus has also been reported (138), implying a neurohormonal link.

Another possible way for central NE to suppress acupuncture analgesia is via the putative inhibitory influence of NE fibers on the raphe nuclei. Thus, degeneration of the NE fibers innervating the raphe magnus nucleus with 6-hydroxydopamine resulted in an augmentation of acupuncture in the rat (139). Furthermore, the nociceptive threshold following injection of phentolamine into the raphe magnus nucleus is elevated (140), indicating a tonic suppressive effect of NE on the raphe system.

The descending bulbo-spinal NE system seems important for morphine analgesia as shown by Takagi and collaborators (141) and others (142, 143). Electrophysiological studies in cats showed that unit discharges recorded from the A1 nucleus in the medulla, which sends NE axons to the spinal cord, were accelerated by EA (129). In contrast to the facilitatory effect of phentolamine when injected intraventricularly (131), intrathecal injection of phentolamine to the rat significantly suppressed the effect of acupuncture (C. W. Xie, J. Tang, J. S. Han, in preparation). It may therefore tentatively be suggested that NE may exert an inhibitory influence in critical nuclei in the brain, while NE projections to the spinal cord mediate the acupuncture effect.

MISCELLANEOUS

Acetylcholine (ACh) has been studied in relation to acupuncture. The intraventricular injection of hemicholinium, an inhibitor of ACh synthesis, caused a dose-dependent attenuation in rats (144, 145). Similar results were obtained when the muscarinic receptors were blocked by atropine in rats (144) or rabbits (7), or by microinjection of scopolamine into the caudate nucleus of the rabbit (146). Choline chloride, the precursor of ACh, exhibited no significant influence *per se* on acupuncture in rats, whereas it partially reversed the suppressive effect of hemicholinium (144). Eserine, at a dose which did not affect the basal tail flick latency significantly, provided a facilitatory action on acupuncture, presumably by increasing the availability of ACh in the CNS (144). All these results suggest a facilitatory role for central ACh in mediating acupuncture analgesia.

Augmentation by different kinds of DA receptor antagonists, droperidol in rats (147), haloperidol (148) or spiroperidol (131) in rabbits, as well as the suppressive effect provided by apomorphine, the DA receptor agonist (131) or L-dopa, the DA percursor, in rabbits (131), suggest that DA may exert an inhibitory effect on acupuncture. This contention is, however, weakened by contradictory reports that haloperidol did not potentiate acupuncture in rat and mice (149), whereas apomorphine did so in rats (149). Neurochemical studies have revealed no significant changes in cerebral DA in rabbits stimulated by EA (49). In rats, there was a general elevation in the cerebral content of DA (51) and its metabolic end-product homovanillic acid (150). However, no correlation was found between the cerebral DA level and the acupuncture effect in rats (51) or in rabbits (49). The role of central DA in acupuncture is therefore still not settled.

Glutamate and γ-aminobutyric acid (GABA) have also been studied with regard to acupuncture. Glutamate seems to facilitate acupuncture in mice (151). Significant increases in GABA transaminase activity are observed in the thalamus and cerebral cortex of the acupuncture responders, and concurrent decreases in GABA and increases in glutamate and glutamine concentrations occur (152). Picrotoxin (153), a GABA antagonist, reduces and diazepam (154), a potentiator of GABA-ergic transmission, enhances acupuncture effectiveness in cats. In these studies, nociceptive discharges were recorded from the trigeminal nucleus, suggesting that GABA inhibit nociceptive neurons in the trigeminal area. Another relevant GABA-ergic pathway may be the habenulo-raphe system which exerts an inhibitory influence on the midbrain raphe (155) and the raphe magnus nucleus (156a).

EA has been reported to reduce cAMP content in the perfusate from caudate nucleus in the rabbit (148) and to lower the cAMP content in the

telercephalon of the rat (156b). Both of these changes were reversed by naloxone (148, 156b). The intraventricular injection of cAMP in rats suppressed the effect of acupuncture analgesia in a dose-dependent manner (157). Radioimmunoassay revealed a marked increase in the cGMP content in lower brain stem and a moderate decrease in the diencephalon, an effect completely reversed by naloxone (156b). In contrast to cAMP, which seemed to exhibit a suppressive effect on acupuncture (157), the intraventricular injection of cGMP potentiated the effect significantly (158), indicating an antagonistic relationship between these nucleotides. A decrease in free Ca^{2+} and increase in Mg^{2+} were noticed in the brain of EA-responding mice (159). Similar changes in the Mg^{2+}/Ca^{2+} ratio were shown after intraventricular injection of aconitine, morphine, or La^{3+}, suggesting common mechanisms for both acupuncture and morphine analgesia (160). A microinjection study revealed that in those brain nuclei where injection of naloxone effectively blocked acupuncture and morphine analgesia, Ca^{2+} presented the same suppressive effect (Z. F. Zhou and J. S. Han, unpublished). These results further support a critical role of Ca^{2+} in pain modulation (161). The nature of these changes is not known.

TOLERANCE TO ACUPUNCTURE ANALGESIA

A phenomenon which is characteristic for acupuncture is the development of tolerance (162). Systematic studies in rats have revealed a gradual fading of the analgesic response during six sessions of EA to about 20% of the original value within 6 hours. A gradual recovery from the tolerance effect was noticed and the original sensitivity returned within approximately 24 hours. Accompanying the development and disappearance of tolerance was a corresponding change in the effectiveness of morphine. In fact, the relation between these two variables was linear and highly correlated. On the other hand, animals made tolerant with injections of increasing doses of morphine for 8 days also developed a parallel degree of tolerance to acupuncture (163). A similar bidirectional cross-tolerance between acupuncture and morphine analgesia occurs in rabbits (164). However, the time-course is different with morphine as the inducer of tolerance, requiring morphine exposure for days (163–165). A report by Cheng et al (166), who found that the analgesic effect elicited by EA was enhanced in mice rendered tolerant to morphine by pellet implantation, seems paradoxical. These experiments were run in mice, and stress-induced analgesia, which has been reported not to show cross-tolerance with morphine analgesia, may have contributed (167, 168, 169). The relative importance of stressful components in different acupuncture models seems worthy of consideration.

There has been extensive research into possible mechanisms for acupuncture tolerance. The phenomenon is reversed by 5-HTP at 200 μg, intraventricularly injected into rats (169) or rabbits, or by 5 μg administered into the nucleus accumbens of the rabbit (164). Comparable studies in cats show that 5-HTP (40–50 mg/kg) reversed the tolerance developed after prolonged brain stimulation (170). It could thus be assumed that functional deficiency of the central 5-HT system might constitute one of the mechanisms for acupuncture tolerance. However, direct assays show the steady-state concentration and the turnover rate of cerebral 5-HT to be higher rather than lower than in the control animals. Furthermore, there was no change in the binding of tritium-labeled 5-HT to receptors in the brain of tolerant rats (169). Thus, changes in release from the presynaptic terminal or binding to the receptors cannot account for the phenomenon, leaving the possibility of a desensitization of the postsynaptic neurons to 5-HT. Supporting this assumption is that other central serotonergic effects, e.g. hypothermia induced by the intraventricular injection of 5-HT, was also reduced in acupuncture tolerant rats (169). Moreover, the effect of acupuncture was significantly attenuated in rabbits made tolerant to 5-HT by repeated intraventricular injection of 5-HTP (164). At the intracellular level a deficiency in the availability of cGMP may account for EA tolerance. A marked elevation in cGMP content in lower brainstem is induced by EA stimulation in naive rats (156b) which could no longer be demonstrated in tolerant rats (169). Moreover the intraventricular injection of cGMP restored the effect of acupuncture analgesia in rats made tolerant to EA after 6 hours of stimulation (169).

Interference with NE mechanisms affects tolerance development. Tolerance which developed after continuous EA in rats could be reversed by intraperitoneal or intraventricular phentolamine or phenoxybenzamine in a dose-dependent manner, but not by propranolol. This agrees with the finding of significant increases of the cerebral content of 3-methoxy-4-hydroxy phenylglycol, a metabolic end-product of central NE, suggesting an increased NE turn-over in acupuncture tolerant rats (C. W. Xie, J. Tang, J. S. Han, in preparation).

The extent and specific character of opiate tolerance have led several investigators to search for anti-opiate substances. Terenius (171) and Ungar et al (172) succeeded in extracting opiate antagonizing material from the brain of animals rendered tolerant to morphine. More recently, Wahlström and Terenius reported on a factor with apparent morphine-antagonistic properties with molecular weight of 1400–3000 daltons from CSF of morphine addicts (173). Han and associates extracted an active factor from the brains of acupuncture tolerant rats, which showed opiate-antagonistic activity in the mouse vas deferens assay. Intraventricular injection of this

factor to rats exhibited marked suppression of both acupuncture and morphine analgesia (174). Several peptides of known structure with morphine-antagonistic properties have been described. Most of them relate to the pro-opiocortin family. ACTH and fragments thereof are antagonistic in a number of tests (175, 176). A fragment of the C-terminal of β-endorphin has also been reported to have anti-opiate activity (177). A critical question in this work is whether or not these peptides act via opioid receptors or indirectly as physiologic antagonists (173).

PAIN RELIEF BY ACUPUNCTURE IN A CLINICAL PERSPECTIVE

The use of acupuncture therapy in various functional disorders goes back several thousand years (1–2). The use of the technique to produce surgical analgesia is of much more recent origin. This application, frequently called acupuncture anesthesia, although pain sensation is fairly selectively affected, developed in China in the late 1950s, where it has also received some popularity as an alternative or adjunct to conventional anesthesia. Not infrequently, one clinic can offer both acupuncture and conventional anesthesia. Also, patients undergoing acupuncture would often receive premedication with benzodiazepines or neuroleptics. Supplementation with analgesics is rarely necessary, demonstrating the potency of the procedure. It may offer advantages in terms of less need for aftercare, but definite studies are lacking (178). In general, it is necessary to use stringent standards in the evaluation of the immediate effects and in follow-up studies, particularly because of difficulties of using double-blind trials. Only well-controlled studies will ultimately lead to improved therapy and an increase in our knowledge of basic pain mechanisms. Here we will only discuss some aspects of the present clinical use of acupuncture within the context of the present review; that is, in the study of its neurochemical mechanisms.

In previous sections we have reviewed studies in humans aimed at the identification of neurochemical substrates which are important in acupuncture, such as endorphins, 5-HT, and NE. This knowledge has, among other things, led to attempts to increase the efficacy and reduce interindividual variability by giving adjuvant therapy with drugs (e.g. 47) which may lead to therapeutic advantages. An area of great promise for the use of acupuncture is in the relief of severe, chronic pain. Pharmacotherapy is frequently inadequate or unacceptable in this condition. Therapeutic results with transcutaneous nerve stimulation are particularly encouraging in patients with chronic neurogenic pain, where pain derives from a lesion of the nervous system, whereas they are less convincing in psychogenic pain or in pain

originating from distinct peripheral somatic lesions such as cancer or arthritis (179, 180). Spinal processes probably contribute substantially to the pain relief, as indicated by changes in spinal fluid levels of various neuronal markers. Patients with neurogenic pain seem to have low endorphin levels (181, 182), low 5-HIAA levels (183), and low substance P levels (184). Substance P is a marker for primary C-fiber afferents involved in pain transmission, but is also found in projections descending to the spinal cord (185). It may therefore be suggested that in chronic neurogenic pain there is inadequate afferent influx which is unable to activate the endogenous pain modulatory systems. Low-frequency electric stimulation can be shown to increase the levels of endorphins acutely over stimulated segments, whereas this is not the case with high-frequency stimulation [(181) and unpublished]. However, more recent studies indicate that the use of high-frequency TNS for several weeks restores the CSF levels of all studied substances to those observed in healthy volunteers (B. Almay, F. Johansson, and L. Terenius, unpublished). The long-term consequences of all types of TNS stimulation therefore seem to be a readjustment to normal conditions.

Morphine and allied drugs are not effective in chronic neurogenic pain (whereas they of course are highly active in severe pain emanating from a peripheral somatic lesion). If the actions of endorphins mimic those of morphine it seems difficult to explain pain relief in chronic neurogenic pain with acupuncture by endorphin activation only. It is more likely that the therapeutic effect of acupuncture can be ascribed to activation of several pain modulatory systems acting in a concerted fashion. Another finding which argues for multiplicatory effects is the long duration of the therapeutic response, which may be days or even weeks. This is hard to understand unless the treatment changes set-points in a homeostatic system, maybe in a fashion which is analogous to that of ECT in depression. The experimental studies reviewed earlier also emphasize the complex nature of the acupuncture effect. In the patient with chronic pain, the proper definition and subdiagnosis of the neuropathology of the individual case needs consideration.

SUMMARY AND CONCLUSIONS

Throughout the history of mankind there has been a search for new and powerful means with which to combat pain, still the most common symptom encountered in the clinic. Physical treatments such as massage and acupuncture, or drugs such as opiates, have been used for a long time. Since acupuncture has been shown to activate central endorphin systems, the similarities between acupuncture and morphine analgesia are plain and

readily explicable. The similarities in action mechanisms are probably more general, extending to, for instance, the descending modulatory 5-HT system.

Although similarities between acupuncture and morphine analgesia prevail, there are also differences. For instance, morphine cannot substitute for acupuncture as a remedy in chronic pain. Acupuncture activates multiple afferent pathways, leading to altered activity in numerous CNS systems. The range of fibers activated will of course depend on the stimulus parameters. High-frequency, low-intensity TNS may mainly activate thick afferents which suppress nociception on a segmental basis (186). Low-frequency stimulation of higher intensity recruits Aδ and C fibers, resulting in a diffuse noxious inhibitory control on dorsal horn convergent neurons (187). In between these two extremes one may find the proper place for classic acupuncture. There is some agreement that classic acupuncture stimulation activates group II, III afferents (21) or Aβ fibers (188, 189) from deep structures, perhaps even Aδ fibers (190) or C fibers (191). One may thus postulate that the "needling sensation" produced by manipulation or electrical stimulation of deep afferents from muscles, tendon, etc. may very effectively contribute to the activation of the endogenous antinociceptive system. For example, no increase of brain enkephalin (192) or β-endorphin (193) was noticed after strong foot shock stimulation, as opposed to the profound increase after acupuncture stimulation (99, 109). While pain produced by ischemia or cold does not release endorphins in humans (194), acupuncture stimulation does.

A certain amount of "stress" is inevitably present during acupuncture stimulation, as is a component of suggestion. However, lack of a relation between the suggestibility and the effectiveness of acupuncture in humans (195) and the susceptibility of almost every laboratory animal to acupuncture argue against the possibility that suggestion plays a dominant role in acupuncture analgesia. Moreover, the ability of naloxone to reverse acupuncture analgesia and its inability to reverse hypnotic analgesia (65) further suggest differences in the mechanisms underlying these manipulations.

At present, the neurochemical and neurophysiological data for the mechanisms of acupuncture analgesia are still fragmentary. 5-HT and NE released by descending pathways at the spinal level and endorphins mainly produced and released locally at the level of the periaqueductal gray, the raphe nuclei, and the spinal cord seem to be the main substrates suppressing the transmission of nociceptive impulses, either by pre- or post-synaptic inhibition. In the lower brain stem, the facilitatory action of endorphins and the inhibitory action of NE on the raphe nuclei constitute a powerful modulatory effect on the descending serotonergic pathway. The habenula has a key role as a relay station between the forebrain structures and the

lower brain stem, and is affected differentially by endorphins and 5-HT on the one hand, and by NE on the other. The involvement of limbic structures such as the nucleus accumbens and the amygdala and their relation to endorphins and 5-HT remain to be elucidated.

The mechanisms for the individual variation in the responsiveness to acupuncture are still puzzling. Recently, a strong correlation was found between the effectiveness of acupuncture (1–3 V, 30 min) and morphine analgesia (3mg/kg, s.c; 113 rats; Z. D. Huang, X. C. Qiu,, and J. S. Han, unpublished). It is highly important to establish whether this individual variation depends on the sensitivity of opioid receptors proper, or on the existence and activity of antiopiate systems. This latter possibility is now under active investigation in several laboratories.

It is still too early to combine these fragments of evidence into a well-defined theory, and much remains to be done to further clarify the mechanisms of this pain-relieving technique used by more than one quarter of the world's population for more than 2,000 years. However, the achievements of the past decade prove that the fine needle has been a powerful lever in promoting the progress of the research on pain and analgesia. We expect it to play this role in the future also.

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Literature Cited

1. Veith, I. 1949. Acupuncture and moxibustion. In *The Yellow Emperor's Classic of Internal Medicine,* pp. 58–76. Baltimore: Williams & Wilkins. 253 pp.
2. Gwei-Dien, L., Needham, J. 1980. A history and rationale of acupuncture and moxa. In *Celestial Lancets.* Cambridge
3. Research Group of Acupuncture Anesthesia, Peking Medical College. 1973. Effect of acupuncture on the pain threshold of human skin. *Nat. Med. J. China* 3:151–57 (In Chinese, English abstr.)
4. Research Group of Acupuncture Anesthesia, Peking Medical College. 1973. Comparison of the analgesic effect of acupuncture and trancutaneous electric stimulation. In *Selected Papers on Theoretical Studies of Acupuncture Anesthesia,* pp. 12–18. Shanghai: People's Press. 264 pp. (In Chinese)
5. Department of Physiology, Shanghai First Medical College. 1973. The effect of acupuncture on the pain threshold of normal humans. See Ref. 4, pp. 33–39
6. Chiang, C. Y., Chang, C. T., Chu, H. L., Yang, L. F. 1973. Peripheral afferent pathway for acupuncture analgesia. *Sci. Sinica* 16:210–17
7. Research Group of Acupuncture Anesthesia, Peking Medical College. 1974. The role of some neurotransmitters of the brain in finger-acupuncture analgesia. *Sci. Sin.* 17:112–30
8. Andersson, S. A., Ericson, T., Holmgren, E., Lindqvist, G. 1973. Electro-acupuncture. Effect on pain threshold measured with electrical stimulation of teeth. *Brain Res.* 63:393–96
9. Chapman, C. R., Gehrig, J. D., Wilson, M. E. 1975. Acupuncture compared with 33% nitrous oxide for dental analgesia. *Anesthesiology* 42:532–37
10. Mayer, D. J., Price, D. D., Rafii, A. 1975. Acupuncture hypalgesia: Evidence for activation of a central control system as a mechanism of action. *First World Congr. Pain, Florence,* p. 276 (Abstr.)
11. Mayer, D. J., Price, D. D., Rafii, A. 1977. Antagonism of acupuncture

analgesia in man by the narcotic antagonist naloxone. *Brain Res.* 121:368–72
12. Jiang, Z. Y., Ye, Q., Shen, Y. T., Zhu, F. X., Tang, S. Q., Liang, N. J., Zeng, X. C. 1978. Effects of naloxone on experimental acupuncture analgesia evaluated by sensory decision theory. *Acta Zool. Sin.* 24:1–8 (In Chinese, English abstr.)
13. Sjölund, B., Eriksson, M. 1979. The influence of naloxone on analgesia produced by peripheral conditioning stimulation. *Brain Res.* 173:295–301
14. Pomeranz, B., Chiu, D. 1976. Naloxone blocks acupuncture analgesia and causes hyperalgesia: Endorphin is implicated. *Life Sci.* 19:1757–62
15. Pomeranz, B., Cheng, R., Law, P. 1977. Acupuncture reduces electrophysiological and behavioral responses to noxious stimuli: Pituitary is implicated. *Exp. Neurol.* 54:172–78
16. Research Group of Acupuncture Anesthesia, Peking Medical College. 1977. Naloxone blockade of acupuncture analgesia in rabbits. *Chin. J. Surg.* 15:192 (In Chinese)
17. Huang, Y., Zhen, J. Z., Li, D. R., Xie, G. Y. 1978. The effect of acupuncture analgesia in monkeys. *Nat. Med. J. China* 4:193–95 (In Chinese)
18. Acupuncture Anesthesia Research Group, Shanghai First Medical College. 1978. The effect of morphine antagonists and morphine tolerance on acupuncture analgesia in rabbits. *Acta Acad. Med. Prim. Shanghai* 5:25–34 (In Chinese, English abstr.)
19. Anderson, S. A. 1979. Pain control by sensory stimulation. In *Advances in Pain Research and Therapy,* ed. J. J. Bonica, J. C. Liebskind, D. G. Albe-Fessard, 3:569–85. New York: Raven. 956 pp.
20. Wall, P. D., Sweet, W. H. 1967. Temporary abolition of pain in man. *Science* 155:108–9
21. Chang, H. T. 1978. Neurophysiological basis of acupuncture analgesia. *Sci. Sin.* 21:829–46
22. Messing, R. B., Lytle, L. D. 1977. Serotonin-containing neurons: Their possible role in pain and analgesia. *Pain* 4:1–21
22a. Kaada, B. 1974. Mechanisms of acupuncture analgesia. *T. Norske Laegeforen.* 94:422–31
23. Research Group of Acupuncture Anesthesia, Shanxi Institute of Traditional Medicine. 1975. The effect of dorsal raphe lesion on acupuncture analgesia in rats. *Shanxi New Med.* 5:59–61 (In Chinese)
24. Yu, G. D., Liu, S. Y., Gao, A. L., Ge, Z. H., Yin, Q. Z., Qian, Z. N., Jian, M. H., Wang, Y. Q., He, B. R., Yin, W. P., Guo, Y. Y., Deng, H. Z. 1979 . Relationship between lip-acupuncture analgesia and serotoninergic neuronal system in the brain. *Nat. Med. J. China* 59:534–38 (In Chinese, English abstr.)
25. Du, H. J., Chao, Y. F. 1976. Localization of central structures involved in descending inhibitory effect of acupuncture on viscero-somatic discharges. *Sci. Sin.* 19:137–48
26. Shen, E., Ma, W. H., Lan, C. 1978. Involvement of descending inhibition in the effect of acupuncture on the splanchnically evoked potential in the orbital cortex of cat. *Sci. Sin.* 21:677–85
27. Chiang, C. Y., Du, H. J., Zhao, Y. F., Gu, X. G., Zhen, R. K., Shan, H. Y., Yang, F. Y. 1977. The effect of lesioning of brain stem raphe nuclei on acupuncture analgesia in the rat. *Nat. Med. J. China* 57:611–17 (In Chinese)
28. Kaada, B., Jorum, E., Sagvolden, T., Ansethwoen, T. E. 1979. Analgesia induced by trigeminal nerve stimulation (electro-acupuncture) abolished by nuclei raphe lesions in rats. *Acupunct. Electrother. Res.* 4:221–34
29. Baumgarten, H. G., Bjorklund, B., Lachenmayer, L., Nobin, A., Stenevi, U. 1972. Long lasting selective depletion of brain 5-HT by 5,6-dihydroxytryptamine. *Acta Physiol. Scand.* 84: Suppl. 373, pp. 1–15
30. Yih, C. C., Wu, S. Q., Yu, Y. G., Wang, F. S., Ji, X. Q., Zhao, D. D., Tsou, K. 1977. The effect on acupuncture analgesia by intraventricular injection of 5,6-dihydroxytryptamine. A functional and fluorescence histochemical study. *Kexue Tongbao* 22:43–48 (In Chinese)
31. Du, H. J., Shen, E., Dong, X. W., Jiang, Z. H., Ma, W. X., Fu, L. W., Jin, G. Z., Zhang, Z. D., Han, Y. F., Yu, L. P., Feng, J. 1978. Effects on acupuncture analgesia by injection of 5,6-dihydroxy tryptamine in cat: A neurophysiological, neurochemical and fluorescence histochemical study. *Acta Zool. Sin.* 24:11–20 (In Chinese, English abstr.)
32. McLennan, H., Gilfillan, K., Heap, Y. 1977. Some pharmacological observations on the analgesia induced by acupuncture in rabbits. *Pain* 3:229–38
33. Nobin, A., Baumgarten, H. G., Bjorklund, B., Lachenmayer, L., Stenevi, U. 1973. Axonal degeneration and regener-

ation of the bulbo-spinal indolamine neurons after 5,6-DHT treatment. *Brain Res.* 56:1–24

34. Han, C. S., Chou, P. H., Lu, C. C., Lu, L. H., Yang, T. H., Jen, M. F. 1979. The role of central 5-hydroxytryptamine in acupuncture analgesia. *Sci. Sin.* 22:91–104
35. Research Group of Acupuncture Anesthesia, Peking Medical College. 1975. The effects of parachlorophenylalanine on acupuncture analgesia in the rabbit. *Kexue Tongboa* 20:483–85 (In Chinese)
36. Han, J. S., Tang, J., Fan, S. G., Zhang, W. Q., Zhe, Q. Z. 1978. Dual control of acupuncture analgesia by central 5-hydroxytryptamine and morphine-like substances. *Nat. Med. J. China* 58: 721–25 (In Chinese, English abstr.)
37. Biochemistry Group, Institute of Acupuncture, Academy of Traditional Chinese Medicine. 1976. The role of central 5-hydroxytryptamine in acupuncture analgesia. *J. New Med. Pharm.* 3: 131–33 (In Chinese)
38. Research Group of Acupuncture Anesthesia, Peking Medical College. 1976. The effect of p-chlorophenylalanine and 5-hydroxytryptophan on acupuncture analgesia in rats. *J. New Med. Pharm.* 3:133–38 (In Chinese)
39. Kin, K. C., Han, Y. F., Yu, L. P., Feng, J., Wang, F. S., Zhang, Z. D., Chang, A. Z., Sheng, M. P., Lu, Y. Y., Shi, K. F., Wang, L. J., Hu, J. W., Wang, L. Q. 1979. Role of brain serotonergic and catecholaminergic systems in acupuncture analgesia. *Acta Physiol. Sin.* 31: 121–32 (In Chinese, English abstr.)
40. Woolf, C. J., Mitchell, D., Barrett, G. D. 1980. Antinociceptive effect of peripheral segmental electric stimulation in the rat. *Pain* 8:237–52
41. Shimizu, L., Fujisaki, M., Koja, T., Kojima, K. 1974. Basic studies on acupuncture analgesia. II. *Folia Pharmacol. Jpn.* 70:167P (In Japanese)
42. Xu, G. S., Zheng, G. C., Shen, E. 1976. Influence of some neuropharmacological agents on the inhibitory effect of acupuncture on viscero-somatic reflexes. *Kexue Tongbao* 21:549–50 (In Chinese)
43. Yin, Q. Z., Huang, W. Q., Quian, Z. N., Zang, Y. Y. 1979. Effect of lysergic acid diethylamide on lip acupuncture analgesia. *Acta Physiol. Sin.* 31:365–70 (In Chinese, English abstr.)
44. Aghajanian, G. K. 1972. LSD and CNS transmission. *Ann. Rev. Pharmacol.* 12: 157–68
45. Research Group of Acupuncture Anesthesia, Peking Medical College. 1975. The effect of pargyline on acupuncture analgesia in the rabbit. *Kexue Tongbao* 20:532–34 (In Chinese)
46. Spector, S., Hirsch, C. W., Brodie, B. B. 1963. Association of behavioral effect of pargyline, a non-hydrazine MAO inhibitor with increase in brain norepinephrine. *Int. J. Neuropharmacol.* 2:81–93
47. Zhao, F. Y., Meng, X. Z., Yu, S. D., Ma, A. H., Dong, X. Y., Han, J. S. 1978. The effect of clomipramine and pargyline on finger-pressing anesthesia for removal of impacted third molar. *J. Beijing Med. Coll.* 2:79–82 (In Chinese)
48. Research Group of Acupuncture Anesthesia, Hunan Medical College. 1973. The relation between acupuncture analgesia and neurotransmitters in the brain. *Nat. Med. J. China* 8:478–86 (In Chinese, English abstr.)
49. Department of Biochemistry, Peking Institute of Tuberculous Diseases. 1977. Changes in the content of central monoamine neurotransmitters during acupuncture analgesia in rabbits. *Acupunct. Anesthesia* 4:60–61 (In Chinese)
50. Ye, W. L., Feng, X. C., Chao, D. F., Chang, J. W., Chang, C. 1979. Effect of electric stimulation of "Du-Channel" point on 5-HT and 5-HIAA contents in the caudate nucleus in the rabbit. *Kexue Tongbao* 24:235–36 (In Chinese, English abstr.)
51. Research Group of Biochemistry, Institute of Acupuncture and Moxibustion, Academy of Traditional Chinese Medicine. 1980. The relationship between acupuncture analgesia and the monoamine transmitters in rat brain. In *Advances in Acupuncture and Acupuncture Anesthesia,* pp. 425–26. Beijing: People's Med. Publ. House. 541 pp.
52. Liang, X. N., Zhang, W. Q., Tang, J., Han, J. S. 1981. Individual variation of acupuncture analgesia in rats in relation to 5-HT and endogenous opiate-like substances in the brain. *Nat. Med. J. China.* 61:345–49 (In Chinese, English Abstr.)
53. Yi, C. C., Lu, T. H., Wu, S. H., Tsou, K. 1977. A study on the release of ^{3}H-5-HT from brain during acupuncture and morphine analgesia. *Sci. Sin.* 20:113–24
54. Du, H. J., Zhao, Y. F. 1981. Modulation of visceral nociceptive reflex by forebrain structures via bulbo-raphe-spinal descending inhibitory system. *Kexue Tongbao* 26:122–25 (In Chinese)

55. Fields, H. L., Basbaum, A. I. 1979. Anatomy and physiology of a descending pain control system. See Ref. 19, pp. 427–40
56. Mayer, D. J., Price, D. D. 1976. Central nervous system mechanisms of analgesia. *Pain* 2:379–404
57. Wu, P. C., Hsu, C. L., Li, T. C., Wu, F. C., Yu, Y. H., Liu, H. C., Chung, K. K. 1979. The effect of electroacupuncture and nociceptive stimulation on unit discharge of nucleus raphe dorsalis in the rat. *Kexue Tongbao* 24:570–73 (In Chinese)
58. Aghajanian, G. K., Rosecrans, J. A., Sheard, M. H. 1966. Serotonin release in the forebrain by stimulation of midbrain raphe. *Science* 156:402–3
59. Sawynok, J., Pinsky, C., Labella, F. S. 1980. Minireview on the specificity of naloxone as an opiate antagonist. *Life Sci.* 25:1621–32
60. Martin, W. R., Eades, C. G., Thompson, G. A., Huppler, R. E., Gilbert, P. E. 1976. The effects of morphine- and nalorphine-like drugs in the nondependent and morphinedependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* 197:517–32
61. Terenius, L., Wahlström, A. 1979. Endorphins in human cerebrospinal fluid as indicators of central endorphin activity. In *Radioimmunology 1979*, ed. Ch. A. Bizollön, pp. 37–44. Amsterdam: Elsevier. 307 pp.
62. Zhou, S. C., Wang, E. Q., Ye, Q., Wang, H., Kang, Y. P. 1980. The influence of acupuncture on the experimental deep and referred pain. See Ref. 51, pp. 367–68
63. Chapman, C. R., Benedetti, C. 1977. Analgesia following transcutaneous electrical stimulation and its partial reversal by a narcotic antagonist. *Life Sci.* 21:1645–48
64. Chapman, C. R., Colpitts, Y. M., Benedetti, C., Kitaeff, R., Gehrig, J. D. 1980. Evoked potential assessment of acupuncture analgesia: Attempted reversal with naloxone. *Pain* 9:183–97
65. Goldstein, A., Hilgard, E. R. 1975. Failure of opiate antagonist naloxone to modify hypnotic analgesia. *Proc. Natl. Acad. Sci. USA* 72:2041–43
66. Barber, J., Mayer, D. 1977. Evaluation of the efficacy and neural mechanism of a hypnotic analgesia procedure in experimental and clinical dental pain. *Pain* 4:41–48
67. Nasrallah, H. A., Holley, T., Janowsky, D. S. 1979. Opiate antagonism fails to reverse hypnotic-induced analgesia. *Lancet* 1:1355
68. Levin, J. D., Gordon, N. C., Fields, H. L. 1979. The role of endorphins in placebo analgesia. See Ref. 19, pp. 547–51
69. Mihic, D., Binkert, E. 1978. Is placebo analgesia mediated by endorphins? *Pain Abstr.* 1:19
70. Sandrew, B. B., Yang, R. C. C. Jr., Wang, S. C. 1977. Electroacupuncture analgesia in monkeys: A behavioral and neurophysiological assessment. *Fed. Proc.* 36:561
71. Huang, Y., Wang, Q. W., Zheng, J., Li, D. R., Xie, G. Y. 1980. Analgesic effect of acupuncture and its reversal by naloxone as shown by the method of operant conditioning response in monkeys. See Ref. 51, pp. 483–84
72. Pomeranz, B., Cheng, R. 1979. Suppression of noxious responses in single neurons of cat spinal cord by electroacupuncture and its reversal by the opiate antagonist naloxone. *Exp. Neurol.* 64:327–41
73. Lu, G. Q., Zhou, Y. Q., Nie, S. H., Lin, N. L. 1980. Effect of electroacupuncture on the viscero-sensory evoked response in mesencephalic central grey of cat and the antagonistic action of naloxone. See Ref. 51, p. 338
74. Shanghai Institute of Materia Medica. 1978. The effect of naloxone on acupuncture analgesia in the rabbit. *Acupunct. Anesthesia* 1:71 (In Chinese)
75. Zhang, A. Z., Xu, S. F., Zeng, D. Y., Zheng, L. M. 1980. The effect of naloxone on acupuncture analgesia produced by different strength of electric stimulation. See Ref. 50, p. 479
76. Cheng, J. S., Ye, Z. J., Ou, S. P. 1979. The effect of naloxone on the inhibitory action of electroacupuncture analgesia upon cortical potentials evoked by tooth pulp stimulation in rabbits. *Nat. Med. J. China* 59:257–60 (In Chinese, English abstr.)
77. Mo, H. Y., Wang, G. N., Yu, G. H., 1979. The action of nalorphine to reverse the inhibitory effect of acupuncture on vascular reaction to visceral stretch. *Nat. Med. J. China* 59:755-58 (In Chinese, English abstr.)
78. Zhou, G. Z., Xu, S. F., Zhang, A. Z. 1980. The effect of naloxazone on electroacupuncture analgesia in rabbits (brief report). *Acupunct. Electrother. Res.* 5:197–99
79. Cheng, R. S. S., Pomeranz, B. H. 1980. Electroacupuncture analgesia is mediated by stereospecific opiate receptors

and is reversed by antagonists of type I receptors. *Life Sci.* 26:631–38
80. Cheng, R. S. S., Pomeranz, B. 1979. Electroacupuncture analgesia could be mediated by at least two pain-relieving mechanisms: Endorphin and non-endorphin systems. *Life Sci.* 25: 1957–62
81. Toda, K. 1978. Effect of electro-acupuncture on rat jaw opening reflex elicited by tooth pulp stimulation. *Jpn. J. Physiol.* 28:485–97
82. Zhu, L. X., Qiao, H. L., Li, C. Y., Fang, Z. R., Li, L. N. 1980. The effect of morphine antagonist on the inhibition of visceralgia by electroacupuncture. See Ref. 51, pp. 389–90
83. Zhou, Z. F., Du, M. Y., Wu, W. Y., Jiang, Y., Han, J. S. 1981. The effect of intracerebral injection of naloxone on morphine analgesia and acupuncture analgesia in rabbits. *Sci. Sin.* 24: 1166–78
84. Sun, F. Y., Xu, M. F., Xu, S. F. 1980. The effects of microinjection of naloxone and p-chloroamphetamine into rabbit central grey on acupuncture analgesia. See Ref. 51, pp. 481-82
85. He, L. F., Du, L. N., Jiang, J. W., Shi, Z. Z., Wang, M. Z. 1980. Effect of naloxone on analgesia from caudate nucleus stimulation in rabbits. See Ref. 51, pp. 480–81
86. Fan, S. G., Tang, J., Ren, M. F., Zhang, W. Q., Liang, X. N., Tu, Z. P., Chen, X. L., Han, J. S. 1980. The effect of injection of naloxone into nucleus accumbens and habenula on acupuncture analgesia in the rat. See Ref. 51, pp. 486–87
87. Ehrenpreis, S., Balagot, R. C., Comaty, J. E., Myles, S. B. 1979. Naloxone reversible analgesia in mice produced by D-phenylalanine and hydrocinnamic acid, inhibitors of carboxypeptidase A. See Ref. 19, pp. 479–88
88. Cheng, R. S. S., Pomeranz, B. 1980. A combined treatment with D-amino acid and electroacupuncture produces a greater analgesia than either treatment alone: Naloxone reverses these effects. *Pain* 8:231-36
89. Han, J. S., Zhang, Y. Z., Tang, J., Zhou, Z. F. 1981. Potentiation of acupuncture analgesia by D-phenylalanine in the rabbit. *Acta Zool. Sin.* 27:133–37 (In Chinese, English abstr.)
90. Zhang, Y. Z., Tang, J., Han, J. S. 1981. Potentiation of electroacupuncture analgesia by bacitracin and D-phenylalanine in mice. *Kexue Tongbao* 26: In press (In Chinese)
91. Zou, K., Yi, Q. C., Wu, S. X., Lu, Y. X., Wang, F. S., Yu, Y. G., Ji, X. Q., Zhang, Z. X., Zao, D. D. 1980. Enkephalin involvement in acupuncture analgesia. *Sci. Sin.* 23:1197–1207
92. Roques, B. P., Zaluski-Fournié, M. C., Soroca, E., Lecomte, J. M., Malfroy, B., Llorens, C., Schwartz, J. C. 1980. The enkephalinase inhibitor thiorphan shows antinociceptive activity in mice. *Nature* 288:286–88
93. Roy, B. P., Cheng, R., Phelan, J., Pomeranz, B. 1980. Pain threshold and brain endorphin levels in genetically obese(Ob/Ob) and opiate receptor deficient(CXBK) mice. In *Endogenous and Exogenous Opiate Agonists and Antagonists,* ed. E. L. Way, pp. 297–300. New York: Pergamon. 570 pp.
94. Cheng, R., Pomeranz, B. 1980. The antipeptidases increase electroacupuncture analgesia and show predictable hypalgesic effects on mice with congenitally abnormal endorphin systems. See Ref. 93, pp. 383–86
95. Peets, J. M., Pomeranz, B. 1978. CXBK mice deficient in opiate receptors show poor electroacupuncture analgesia. *Nature* 273:675–76
96. Cheng, R., Pomeranz, B., Yu, G. 1979. Dexamethasone partially reduces and 2% saline treatment abolishes electroacupuncture analgesia: These findings implicate pituitary endorphins. *Life. Sci.* 24:1481–86
97. Tang, J., Wang, Y., Yang, X. D., Han, J. S. 1981. The role of pituitary opioids in electroacupuncture analgesia in the rat. *J. Beijing Med. Coll.* 13:202–4 (In Chinese, English abstr.)
98. Yi, C. C., Yu, Y. G., Ji, X. Q., Zou, K. 1978. Preliminary studies on the discharge of endorphine from pituitary after electric acupuncture. *Nat. Med. J. China* (7):397–98 (In Chinese)
99. Tang, J., Han, J. S. 1978. Changes in the morphine-like activity in rat brain and pituitary gland during electroacupuncture analgesia. *J. Beijing Med. Coll.* (3):150–52 (In Chinese)
100. Peng, L. H. C., Yang, M. M. P., Kok, S. H., Woo, Y. K. 1978. Endorphin release: A possible mechanism of acupuncture analgesia. *Comp. Med. East West* 6:57–60
101. Yang, M. M. P., Kok, S. H. 1979. Further study of the neurohumoral factor, endorphin, in the mechanism of acupuncture analgesia. *Am. J. Chin. Med.* 7:143–48
102. Chen, M. Q., Zheng, Y. F., Xue, Z. H., Wen, Y. Y., Nie, Z. M., Zhang, B. Z.

1980. A study on the role of humoral factors in the central action of acupuncture analgesia. See Ref. 51, pp. 424–45
103. Kastin, A. J., Olsen, R. D., Schally, A. V., Coy, D. H. 1979. CNS effects of peripherally administered brain peptides. *Life Sci.* 25:401–24
104. Hosobuchi, Y., Li, C. H. 1978. A demonstration of the analgesic activity of human β-endorphin in six patients. *Pain Abstr.* 1:18
105. Buscher, H. H., Hill, R. C., Romer, D., Cardinaux, F., Closse, A., Hauser, D., Pless, J. 1976. Evidence for analgesic activity of enkephalin in the mouse. *Nature* 261:423–25
106. Bergland, R. M., Page, R. B. 1978. Can the pituitary secrete directly to the brain (affirmative anatomical evidence). *Endocrinology* 102:1325–28
107. Deleted in press
108. Millan, M. J., Przewlocki, R., Herz, A. 1980. A non-β-endorphinergic adenohypophysial mechanism is essential for an analgesic response to stress. *Pain* 8:343–53
109. Amir, S., Amit, Z. 1978. The pituitary gland mediates acute and chronic pain responsiveness in stressed and non-stressed rats. *Life Sci.* 24:439–48
110. Murai, T. M., Tanaka, M., Hachisu, M., Oka, K., Takeshige, C. 1979. The relationship between individual variation of effectiveness of acupuncture analgesia and endogenous morphine like factor. *Neurochem. Res.* 4:666–67
111. Zhang, W. Q., Liang, X. N., Tang, J., Han, J. S. 1980. The relationship between acupuncture analgesia and the activity of opiate like substances in different brain areas in rats. See Ref. 51, pp. 484–85
112. Chen, Q. S., Tang, J., Han, J. S. 1981. Increase of β-endorphin content in brain and pituitary during acupuncture analgesia in rats. *Kexue Tongbao.* 26:832 (In Chinese)
113. Ho, W. K. K., Wen, H. L., Lam, S., Ma, L. 1978. The influence of electroacupuncture on naloxone-induced morphine withdrawal in mice: Elevation of brain opiate-like activity. *Eur. J. Pharmacol.* 49:197–99
114. Wen, H. L., Ho, W. K. K., Ling, N., Ma, L., Chao, G. H. 1979. The influence of electroacupuncture on naloxone-induced morphine withdrawal. II. Elevation of immunoassayable β-endorphin activity in the brain but not in the blood. *Am. J. Chin. Med.* 7:237–40
115. Sjolund, B., Terenius, L., Eriksson, M. 1977. Increased cerebro-spinal fluid levels of endorphins after electroacupuncture. *Acta Physiol. Scand.* 100:382–84
116. Acupuncture Anesthesia Research Coordinating Group, Shanghai First Medical College. 1978. The relationship between the human CSF levels of morphine-like substances and acupuncture analgesia (a preliminary report). *Acta Acad. Med. Prim. Shanghai* 5:13–16 (In Chinese, English abstr.)
117. Wahlström, A., Terenius, L. 1980. Chemical characteristics of endorphins in human cerebrospinal fluid. *FEBS Lett.* 118:241–44
118. Pan, X. P., Lou, X. H., Yao, S. Y., Jian, S. Y., Du, G. Z., Gao, H., Jian, C. C., Jiang, W. X. 1980. The relationship between the human CSF levels of endorphins and acupuncture analgesia. See Ref. 51, pp. 477–78
119. Acupuncture Anesthesia Research Group, Shanghai First Medical College. 1978. Studies on the morphine-like substances in the human brain. *Nat. Med. J. China* 10:611–16 (In Chinese, English abstr.)
120. Clement-Jones, V., McLoughlin, L., Tomlin, S., Besser, G. M., Rees, L. H., Wen, H. L. 1980. Increased β-endorphin but not met-enkephalin levels in human CSF after acupuncture for recurrent pain. *Lancet* 2:946–49
121. Clement-Jones, V., Lowry, P. J., McLoughlin, L., Besser, G. M., Rees, L. H., Wen, H. L. 1979. Acupuncture in heroin addicts: Changes in met-enkephalin and β-endorphin in blood and CSF. *Lancet* 2:380–83
122. Zhang, A. Z., Huang, D. K., Zeng, D. Y., Zhang, L. M., Wang, D. L., Zhu, G. G. 1981. The changes of endorphins in perfusate of certain nuclei in rabbits during acupuncture analgesia. *Acta Physiol. Sin.* 33:8–16 (In Chinese, English abstr.)
123. Han, J. S., Tang, J., Fan, S. G., Jen, M. F., Zhou, Z. F., Zhang, W. Q., Liang, X. N. 1980. Central 5-hydroxytryptamine, opiate-like substances and acupuncture analgesia. See Ref. 93, pp. 395–98
124. Zhao, J. C., Yen, Y. L., Zhang, Q. Z., Li, Z. L. 1964. The effect of electroacupuncture on norepinephrine content in the rat brain. *Proc. Ann. Meet. Chin. Soc. Physiol. Sci.* Dalian, p. 169 (In Chinese)
125. Ng, L. K. Y., Thoa, N. B., Dothitt, T. C., Albert, C. A., Viktora, J. 1974. Decrease in brain neurotransmitters and elevation of footshock-induced pain threshold following repeated electro-

stimulation of putative acupuncture loci in rats. *Am. J. Chin. Med.* 2:336–37
126. Han, J. S., Guan, X. M., Shu, J. M. 1979. Study of central norepinephrine turnover rate during acupuncture analgesia in the rat. *Acta Physiol. Sin.* 31:11–19 (In Chinese, English abstr.)
127. Dong, X. W., Jian, Z. H., Fu, L. W. 1978. Changes in monoamine fluorescence intensity in the rat's midbrain raphe nuclei and locus coeruleus in the process of acupuncture analgesia. *Acta Biochem. Biophys. Sin.* 10:119–25 (In Chinese, English abstr.)
128. Wu, B. J., Wu, F. J., Xu, L. R., Wu, H. Z. 1980. The effect of electroacupuncture on the unit discharge of rat locus coeruleus. See Ref. 51, p. 356
129. Xie, Y. K. 1981. The effect of monoamines and acupuncture on neuronal activity in Al nuclei region of medulla in cats. *Acta Physiol. Sin.* 33:30–35 (In Chinese, English abstr.)
130. Su, S. Y., Han, J. S., Zhai, Q. Z., Liang, X. N., Tang, J., Ren, M. F., Wu, W. Y. 1980. The effect of dihydroxyphenylserine on acupuncture analgesia in the rat: α and β adrenergic receptors implicated. See Ref. 51, pp. 451–52
131. Han, J. S., Ren, M. F., Tang, J., Fan, S. G., Xu, J. M., Guan, X. M. 1979. The role of central catecholamines in acupuncture analgesia. *Chin. Med. J.* 92:793–800
132. Department of Anesthesiology, First Affiliated Hospital, Peking Medical College. 1976. The possible implication of β-adrenergic receptors in acupuncture anesthesia. A preliminary report. *Acupunct. Anesthesia* 1:69–71 (In Chinese)
133. Ungerstedt, U. 1971. Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta Physiol. Scand.* 83: Suppl. 367, pp. 1–48
134. Zhao, J. C., Huang, Y. Y., Li, C. M. 1980. Effects of catecholaminergic neurons of CNS in acupuncture analgesia. See Ref. 51, pp. 450–51
135. Du, H. J., Chao, Y. F. 1979. Effect of destruction or stimulation of locus coeruleus on inhibition of viscero-somatic reflex activities. *Acta Physiol. Sin.* 31:153–62 (In Chinese, English abstr.)
136. Zhang, D. X., Pai, Y. H., Gu, X. G., Shan, H. Y., Wu, W. L., Chiang, C. Y. 1978. Effects of lesions placed on Loci Coeruleus or dorsal noradrenergic ascending bundles on acupuncture analgesia in rats. *Kexue Tongbao* 23:117–21 (In Chinese)
137. Zhou, Z. F., Du, M. Y., Wu, W. Y., Han, J. S. 1981. Effect of intracerebral injection of clonidine or phentolamine on acupuncture analgesia in rabbits. *Acta Physiol. Sin.* 33:1–7 (In Chinese, English abstr.)
138. Pan, G. C., Zhang, S. M. 1980. Effect of microinjection of noradrenaline into hypothalamus on acupuncture analgesia. See Ref. 51, p. 455
139. Tung, H. W., Chiang, C. H., Fu, L. W. 1979. Influence of intracerebral injection of 6-hydroxydopamine on acupuncture analgesia and monoaminergic neurons' histofluorescence of dorsal raphe nucleus. *Acta Physiol. Sin.* 31:273–80 (In Chinese, English abstr.)
140. Hammond, D. L., Levy, R. A., Proudfit, H. K. 1980. Hypoalgesia following microinjection of noradrenergic antagonists in the nucleus raphe magnus. *Pain* 9:85–102
141. Shiomi, H., Takagi, H. 1974. Morphine analgesia and the bulbo-spinal noradrenergic system: Increase in the concentration of normetanephrine in the spinal cord of the rat caused by analgesics. *Br. J. Pharmacol.* 52:519–26
142. Martin, G. F., Humbaston, A. O. Jr., Laxson, C., Panneton, W. M. 1979. Dorsolateral pontospinal system. Possible routes for catecholamine modulation of nociception. *Brain Res.* 163: 333–38
143. Zemlan, F. P., Corrigan, S. A., Pfaff, D. W. 1980. Noradrenergic and serotonergic modulation of spinal analgesia mechanisms. *Eur. J. Pharmacol.* 61: 111–24
144. Ren, M. F., Tu, Z. P., Han, J. S. 1980. The effect of hemicholine, choline, eserine and atropine on acupuncture analgesia in the rat. See Ref. 51, pp. 439–40
145. Guan, X. M., Yu, B., Wang, D., Wang, C. Y., Liu, X. C. 1980. Influence of eserine, acetylcholine and hemicholine-3 on the electroacupuncture analgesia. See Ref. 51, pp. 441–42
146. Ho, L. F., Ho, X. F., Si, C. Z. 1979. Effect of intracaudate microinjection of scopolamine on electroacupuncture analgesia in the rabbit. *Acta Physiol. Sin.* 31:47–52 (In Chinese, English abstr.)
147. Research Group of Acupuncture Anesthesia, Peking Medical College. 1976. Effect of droperidol on acupuncture analgesia in rats. *J. Peking Med. Coll.* 2:75–79 (In Chinese)
148. Xu, S. F., Li, W. B., Sheng, M. P., Zhang, L. M., Zeng, D. Y. 1980. The

cAMP level in caudate perfusate during acupuncture analgesia. *Acta Physiol. Sin.* 32:238–44 (In Chinese, English abstr.)

149. Huang, L., Gui, Y. 1980. The role of intracerebral catecholamines on acupuncture analgesia. See Ref. 51, pp. 455–56
150. Yang, F. Z., Xiu, J., Kin, K. Z., Yu, L. P., Han, Y. F. 1980. Role of brain dopamine system in rabbits' acupuncture analgesia. *Acta Physiol. Sin.* 32:345–50 (In Chinese, Eng. abstr.)
151. Department of Biology, Nanking University. 1978. The role of brain ammonia in electroanalgesia. *Acta Zool. Sin.* 24:136–42 (In Chinese, English abstr.)
152. Chu, C. C., Tsung, Y. Y., Kung, M. E., Hung, Y. P., Chen, C. 1979. Effect of electroacupuncture analgesia on the free amino acid content in the brain of the mice. *Kexue Tongbao* 24:45–46 (In Chinese, English abstr.)
153. Department of Physiology, Kirin Medical College. 1977. The inhibition effect and the mode of action of electroacupuncture upon discharges from the pain sensitive cells in spinal trigeminal nucleus. *Sci. Sin.* 20:485–501
154. Wang, S., Jiang, Y., Fu, F. H., Ma, Z. Y., Liu, M. Z. 1980. Observation on the effect of diazepam on the enhancement of presynaptic inhibition to promote the effect of acupuncture analgesia. See Ref. 51, p. 347
155. Wang, R. Y., Aghajanian, G. K. 1977. Physiological evidence for habenula as major link between fore brain and midbrain raphe. *Science* 197:89–91

156a. Wang, S., Jian, Y., Xiao, J. S., Liu, M. Z., Liu, S. P. 1980. Spontaneous discharges of habenula and its inhibitory action on nucleus raphe magnus. *Kexue Tongbao* 25:36–39 (In Chinese)

156b. Xu, C., Yang, C. L., Liu, S. Y., Wang, J. L., Liang, K., Li, S. J., Tang, J., Han, J. S. 1981. The effect of electroacupuncture on cAMP and cGMP concentrations in whole brain and discrete brain areas of the rat. *J. Beijing Med. Coll.* 13:31–33 (In Chinese, English abstr.)

157. Qiu, X. C., Jia, G. L., Han, J. S. 1979. The effect of intraventricular injection of cAMP on acupuncture analgesia and morphine analgesia in the rat. *J. Beijing Med. Coll.* 1:4–6(In Chinese)
158. Qiu, X. C., Jia, G. L., Ho, X. Z., Han, J. S. 1981. Augmentation of acupuncture analgesia by intraventricular injection of cGMP in the rat. *Nat. Med. J. China* 61:225–28 (In Chinese, English abstr.)
159. Chang, T. H., Chen, R. S. 1979. Relationship of calcium and magnesium contents in thalamus on electroacupuncture analgesia. *Kexue Tongbao* 24:475–77 (In Chinese, English abstr.)
160. Zhang, Z. X., Zhang, Y. Z., Yu, Q. X., Li, C. B., Chen, R. S. 1980. The common ionic basis of electric acupuncture analgesia and morphine analgesia. *Kexue Tongbao* 25:375–78 (In Chinese, English abstr.)
161. Chapman, D. B., Way, E. L. 1980. Metal ion interactions with opiates. *Ann. Rev. Pharmacol. Toxicol.* 20: 553–79
162. Ren, M. F., Han, J. S. 1979. Rat tail flick acupuncture analgesia model. *Chin. Med. J.* 92:576–82
163. Han, J. S., Li, S. J., Tang, J. 1981. Tolerance to acupuncture and its cross tolerance to morphine. *Neuropharmacology* 20:593–96
164. Xuan, Y. T. 1981. *The role of central 5-hydroxytryptamine in acupuncture analgesia in the rabbit.* BSc thesis. Beijing Med. Coll., Beijing. 88 pp.
165. Tang, J., Liang, X. N., Zhang, W. Q., Han, J. S. 1979. Acupuncture tolerance and morphine tolerance in rats. *Beijing Med.* 1:34–37 (In Chinese)
166. Cheng, R., Pomeranz, B., Yu, G. 1980. Electroacupuncture hypalgesia is enhanced in morphine dependent mice; Showing no cross-tolerance and reducing signs of withdrawal. See Ref. 93, pp. 533–35
167. Akil, H., Watson, S. J., Berger, P. A., Barchas, J. D. 1978. Endorphins, β-lipotropin and ACTH: Biochemical pharmacological and anatomical studies. *Adv. Biochem. Psychopharmacol.* 18:125–47
168. Przewlocki, R., Millan, M. J., Herz, A., 1980. Is β-endorphin involved in the analgesia generated by stress. See Ref. 93, pp. 391–94
169. Li, S. J. 1981. *The role of central 5-hydroxytryptamine and cGMP in acupuncture analgesia in the rat.* BSc thesis. Beijing Med. Coll., Beijing. 97 pp.
170. Oliveras, J. L., Hosobuchi, Y., Guilbaud, G., Besson, J. M. 1978. Analgesic electrical stimulation of feline nucleus raphe magnus: Development of tolerance and its reversal by 5-HTP. *Brain Res.* 146:404–9
171. Terenius, L. 1975. Opiate receptors and their ligands. *Proc. 6th Int. Congr. Pharmacol.* 1:153–63

172. Ungar, G., Ungar, A. L., Malin, D. H., Sarantakis, D. 1977. Brain peptides with opiate antagonist action: Their possible role in tolerance and dependence. *Psychoneuroendocrinology* 2: 1–10
173. Wahlström, A., Terenius, L. 1980. Factor in human CSF with apparent morphine-antagonistic properties. *Acta Physiol. Scand.* 110:427–29
174. Han, J. S., Tang, J., Huang, B. S., Liang, X. N., Zhang, W. Q. 1980. Acupuncture tolerance in rats: Anti-opiate substrates implicated. *Chin. Med. J.* 92:625–27
175. Gispen, W. H., Buitelaar, J., Wiegant, M. V., Terenius, L., de Wied, D. 1976. Interaction between ACTH fragments, brain opiate receptors and morphine-induced analgesia. *Eur. J. Pharmacol.* 39:393–97
176. Smock, T., Fields, H. L. 1981. ACTH (1–24) antagonizes opiate-induced analgesia in the rat. *Brain Res.* 212:202–06
177. Lee, N. M., Friedman, J. J., Leybin, L., Cho, T. M., Loh, H. H., Li, C. H. 1980. Peptide inhibitor of morphine and β-endorphin-induced analgesia. *Proc. Natl. Acad. Sci. USA* 77:5525–26
178. Eriksson, M. B. E., Sjölund, B. H., Nielzén, S. 1979. Long term results of peripheral conditioning stimulation as an analgesic measure in chronic pain. *Pain* 6:335–47
179. Bonica, J. J., 1974. Acupuncture anesthesia in the People's Republic of China. *J. Am. Med. Soc.* 229:1317–25
180. Johansson, F., Almay, B. G. L., Von Knorring, L., Terenius, L. 1980. Predictors for the outcome of treatment with high frequency transcutaneous electrical nerve stimulation in patients with chronic pain. *Pain.* 9:55–61
181. Terenius, L. 1981. Endorphins and pain. *Front. Horm. Res.* 8:162–77
182. Almay, B. G. L., Johansson, F., von Knorring, L., Terenius, L., Wahlström, A. 1978. Endorphins in chronic pain. I. Differences in CSF endorphin levels between organic and psychogenic pain syndromes. *Pain* 5:153–62
183. Almay, B. G. L., Johansson, F., von Knorring, L., Sedvall, G., Terenius, L. 1980. Relationships between CSF levels of endorphins and monoamine metabolites in chronic pain patients. *Psychopharmacology* 67:139–42
184. Terenius, L. 1981. Endorphins, substance P and clinical pain. *Proc. Int. Narcotic Res. Conf., Kyoto.* In press
185. Hökfelt, T., Ljungdahl, Å., Terenius, L., Elde, R., Nilsson, G. 1977. Immunohistochemical analysis of peptide pathways possibly related to pain and analgesia: Enkephalin and substance P. *Proc. Natl. Acad. Sci. USA* 74:3081–85
186. Melzack, R., Wall, P. D. 1965. Pain mechanisms: A new theory. *Science* 150:971–79
187. Le Bars, D., Dickenson, A. H., Besson, J. M. 1979. Diffuse noxious inhibitory controls (DNIC). *Pain* 6:283–327
188. Lu, G. W., Liang, R. Z., Xie, J. Q., Wang, Y. S., He, G. R. 1979. Role of peripheral afferent nerve fiber in acupuncture analgesia by needling point Zusanli. *Sci. Sin.* 22:680–92
189. Toda, K., Ichioda, M., Iriki, A. 1980. Effective conditions of electroacupuncture stimulation for suppressing tooth pulp evoked jaw-opening reflex in the rat. *Bull. Tokyo Med. Dent. Univ.* 27:111–19
190. Shao, T. H., Wu, C. P., Chao, C. C. 1979. Afferent nerve fibers activated by the same nerve electric acupuncture. *Kexue Tongbao* 24:329–30 (In Chinese, English abstr.)
191. Chen, L. S., Tang, J. S., Yen, J. Q. 1980. Analysis of the afferent fiber for acupuncture analgesia. *Kexue Tongbao* 25:763–65 (In Chinese)
192. Fratta, W., Yang, H. Y. T., Hong, J., Costa, E. 1977. Stability of met-enkephalin content in brain structures of morphine-dependent and of footshock stressed rats. *Nature* 268:452–53
193. Rossier, J., French, E. D., Rivier, C., Ling, N., Guillemin, R., Bloom, F. E. 1977. Foot-shock induced stress increase β-endorphin levels in blood but not brain. *Nature* 270:618–20
194. Grevert, P., Goldstein, A. 1978. Endorphins: Naloxone fails to alter experimental pain or mood in humans. *Science* 199:1093–95
195. Xu, S. L., Fu, Z. L., Tang, J., Han, J. S. 1980. The effect of acupuncture and its relation to blood endorphin, blood histamine and suggestibility. *Acup. Res.* 5:273–81