

Review

How Do Acupuncture and Moxibustion Act? – Focusing on the Progress in Japanese Acupuncture Research –

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Abstract. The mechanisms of action of acupuncture and moxibustion as reported by Japanese researchers are reviewed. The endogenous opioid-mediated mechanisms of electroacupuncture (EA) as used in China are well understood, but these are only one component of all mechanisms of acupuncture. These studies emphasize the similarity of the analgesic action of EA to various sensory inputs to the pain inhibition mechanisms. In Japanese acupuncture therapy, careful detection of the acupuncture points and fine needling technique with comfortable subjective sensation are considered important. The role of polymodal receptors (PMR) has been stressed based on the facts that PMRs are responsive to both acupuncture and moxibustion stimuli, thermal sensitivity is essential in moxibustion therapy, and the characteristics of acupuncture points and trigger points are similar to those of sensitized PMRs. Acupuncture and moxibustion are also known to affect neurons in the brain reward systems and blood flow in skin, muscle, and nerve. Axon reflexes mediated by PMRs might be a possible mechanism for the immediate action of acupuncture and moxibustion. Reports on the curative effects of acupuncture on various digestive and urological disorders are also reviewed briefly.

Keywords: acupuncture and moxibustion, polymodal receptor, endogenous opioid, reward system, somato-autonomic reflex

Introduction

Recent interest in complementary and alternative medicine (CAM) has promoted research on various procedures for healing and health care. According to the National Center of Complementary and Alternative Medicine (NCCAM) classification, CAM includes various types of psychological and physical procedures, foods, supplements, and traditional medical treatments such as traditional Chinese medicine. Acupuncture and moxibustion therapy are also considered to be important fields in CAM.

Among the numerous CAM therapies, acupuncture,

and moxibustion have been the subjects of research based on modern medical methodology for a long time. Research on the mechanisms of acupuncture action actually started around 1950. Numerous reports on the miracle success of various surgical operations with acupuncture needling surprised clinicians and basic researchers throughout the world, and the analgesic effect of acupuncture needling became the initial target of investigation. An important pharmacological study was published by a research group at Peking University. They demonstrated that the analgesic effect of acupuncture stimulation develops gradually with a 15 to 20 min induction time and appears over the whole tested body surface. Based on a time course analysis of the analgesic effects, they proposed the participation of chemical substances in the analgesic actions of acupuncture (1).

Electroacupuncture (EA) is electrical stimulation through the acupuncture needles with short current

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pulses at different frequencies. Han has clearly demonstrated that EA induces an analgesic effect in conscious rats. Furthermore, it was suggested that various endogenous opioids such as β endorphin, enkephalin, and dynorphin are involved in electroacupuncture analgesia (EAA). This working hypothesis about the role of endogenous opioids in acupuncture action has been widely accepted (2). The details of the research on this matter will be introduced in a later section because it is difficult to review the pharmacological mechanisms of acupuncture action without that evidence.

It should be noted, however, that the endogenous opioid hypothesis of acupuncture action was established on the basis of acute experiments with normal experimental animals. The hypothesis could explain phenomena such as EAA for surgical operations and why EAA requires an induction time of at least ten minutes. However, in acupuncture clinics in Japan, patients with symptoms of pain who are treated by acupuncture and moxibustion usually obtain pain relief immediately after treatment with gentle manipulation of a fine needle. It is therefore obvious that different mechanisms should be considered for the explanation of the immediate effect of the gentle Japanese style of acupuncture. Another important point to be noted is that pain relief is not the only symptom that can be treated by acupuncture and moxibustion. These procedures work on various disorders of internal diseases. Anti-emetic effects of acupuncture have been well-evaluated, and it was listed at the top of the NIH consensus development statement (3).

Acupuncture and moxibustion therapy in Japan has a long history, and it developed differently from the Chinese procedures. The use of a guide tube for the insertion of a fine acupuncture needle without pain is a Japanese technique. Acupuncture and moxibustion have been ignored by the modern medical system in Japan since the Meiji era. Licensed acupuncture and moxibustion specialists have been educated outside of modern medical schools, and the majority of acupuncture treatments have been done in private acupuncture clinics rather than in hospitals. Education, licensure, and insurance systems made it difficult to develop scientific research on acupuncture and moxibustion in Japan. In 1983, the Meiji University of Oriental Medicine was established as the first special school for education and research in acupuncture and moxibustion. A 4-year course is standard. Then, a university hospital was opened and a graduate school for masters and doctors degrees in acupuncture and moxibustion was established.

In this review, we discuss the progress of acupuncture research conducted by Japanese researchers and relate

that work to other classical and recent literature on acupuncture action. The major topics in this review are the physiological basis of acupuncture points and its relation to the polymodal receptor (PMR), which is part of an afferent pathway for acupuncture and moxibustion stimulation. Analgesic effects induced by acupuncture, including the actions of endogenous opioids and diffuse noxious inhibitory controls (DNIC), are also discussed. Effects of acupuncture and moxibustion on the higher central nervous system (CNS), with a special focus on the changes in the neurotransmitters in the reward systems, are considered. Finally, effects of acupuncture and moxibustion on autonomic functions, such as changes in tissue blood flow and digestive and urological functions, are reviewed.

Receptors and afferent fibers responsible for modes of action of acupuncture and moxibustion

It is of fundamental importance to identify the receptors and afferent fibers that are specifically involved in the mechanisms of acupuncture and moxibustion. It is very difficult to determine the receptors and afferent fibers involved because various mechanoreceptors and thermal receptors could be activated by acupuncture and moxibustion for example.

Single unit recordings were made in rats responding to manual acupuncture (MA) stimulation and every somatosensory afferent (groups I, II, III, and IV) was activated (4). The group I and II afferents, the best responders to MA, did not respond to the thermal stimulation of moxibustion. Thermal and heat receptors responded to moxibustion but not to mechanical stimulation. In the early stages of investigation of the peripheral mechanisms of acupuncture action, the thick A-beta afferent fiber received much attention because the analgesic action of acupuncture stimulation was the major issue to be clarified and the gate control hypothesis was an attractive theoretical basis for analgesic action (5). Activation of thick afferent fibers inhibits pain signal transmission at the spinal cord. This analgesic action of thick fibers was confirmed clinically. A procedure for pain relief based on the gate control theory was called transcutaneous electrical nerve stimulation (TENS) (6). If we assume that EA is a kind of nerve stimulation procedure, it is very easy to explain the physiological mechanism of EAA.

It is important to note that acupuncture and moxibustion have been used clinically for over 2000 years, and each is based on the same meridian theory. However thick fiber mechanoreceptors can not be activated by thermal stimulations such as moxibustion. Moreover an important fact was discovered in the survey of the

ancient Chinese tomb called *Ma-Wang-Dui*. The medical literature found in the tomb clearly demonstrated that the meridian concepts were established based on moxibustion therapy and that no acupuncture treatment existed when the meridian concept was born (7). Therefore we should consider candidate nerves that are activated by moxibustion as being the primary peripheral mediators of both procedures. We could not completely exclude the roles of mechanoreceptors in the production of analgesia via gate control mechanisms; however, it should be stressed that our understanding of the fundamental mechanism of acupuncture and moxibustion is based on moxibustion-sensitive inputs.

A specific sensation elicited by acupuncture stimulation called “de-qi”

When acupuncture or moxibustion is applied to patients, a specific sensation called “*de-qi*” is induced. This *de-qi* sensation is thought to be essential for the effects of acupuncture and moxibustion; however, the responsible receptors and afferent fibers have not been identified. Injection of local anesthetics into a muscle nerve bundle innervating the *Ho-ku* (LI4) acupuncture points completely abolished the *de-qi* induced by acupuncture manipulation, but the *de-qi* was not abolished by anesthetizing a cutaneous nerve (8).

To clarify the characteristics of afferent fiber receptors responsible for the production of the *de-qi* sensation, microneurography was used. Recordings of nerve discharges in human subjects make it possible to investigate the quality of subjective sensation and identify the responsible afferent fiber receptors. A close correlation between a particular *de-qi* sensation and the excitation of thin afferent fibers responsive to bradykinin (BK) was demonstrated. Discharges of PMRs in deep tissue and a *de-qi* sensation were provoked simultaneously by MA, and the frequencies of discharges were well correlated with the intensities of *de-qi* sensations (9). Another important fact was reported by Ochoa. Namely, his group developed a microstimulation technique (a method of electrical stimulation of an identified single unit through a fine metal recording electrode) that enabled a clear demonstration that painful sensation is not provoked by microstimulation of C fiber afferents at frequencies less than 2 Hz, although it was shown that a higher frequency stimulation produces a strong painful burning sensation (10). These results indicate that the *de-qi* sensation is evoked by excitation of the PMR and suggest that we can not exclude the participation of the PMR in the Japanese style of fine acupuncture needling because low discharge frequency might induce some physiological effects in subjects without any *de-qi*

sensation.

Characteristics of acupuncture points and tender /trigger points

The fundamental problem to be solved in acupuncture and moxibustion research is to clarify the nature of so-called acupuncture points. The fact that there is no specific structure or distribution of acupuncture points to various tissues on the whole body is important (11). In Chinese traditional textbooks, the “*ah-shi-point*”, where the patient shouts “oh painful” when the acupuncture needle hits the point, was described as a kind of acupuncture point. That is, tenderness is one of the clearest physiological characters of acupuncture points. Our previous survey also clearly demonstrated that tender points as well as acupuncture points were used in clinical treatment by well-trained Japanese acupuncturists (12).

Trigger points have been well documented in patients with myofascial pain syndrome (MPS). Trigger points are characterized by their tenderness to applied pressure, tenderness at the restricted point on the palpable band, and their induction of specific referred pain phenomena similar to that which the subject has suffered (13). There is a very interesting concordance of the location of the acupuncture points and the trigger points. Melzack reported that the trigger points in MPS patients were in high concordance with those of the acupuncture points (14). The concept of the trigger points was established from the modern Western medical treatment of pain without any knowledge of traditional Chinese medicine. The distribution of tender points in patients with fibromyalgia was also shown to be quite similar to that of acupuncture points (15). These similarities of location of trigger and/or tender points to those of acupuncture points suggest that a common pathophysiological mechanism might exist.

Mechanism of formation of tender/trigger points

The sensitization of nociceptors such as the PMRs has been considered the most probable mechanism of formation of tender points (16). However, several working hypotheses have been proposed for the pathogenesis of trigger points because of their complicated characteristics. One of the most famous hypotheses is the contracture and energy crisis mechanism proposed by Travell and Simons (13). Minor injury of muscle tissues induces the release of calcium ions from the endoplasmic reticulum of the muscle cell, and these trigger the contraction of muscle without electrical activation of the muscle membrane. The muscle contrac-

ture suppresses the oxygen supply to the muscle, and the ischemia leads to release of various chemicals that sensitize the nociceptors (17). However, Hubbard clearly demonstrated that spontaneous electrical activities (SEAs) could be recorded from active trigger points in MPS patients, and he assumed the SEAs were the electrical activities of intrafusal muscles in the muscle spindle (18). After this new finding, Simon proposed a new integrated hypothesis. Release of excess acetylcholine from the motor endplate produces endplate spikes and contraction knots under the endplate. The continuous contraction causes local ischemia and several chemical substances are released that may sensitize the nociceptors such that trigger points are formed (19). Recently, the increments of various sensitizing chemicals such as prostaglandins (PGs), histamine, and BK were detected with a microdialysis technique at active trigger points in humans (20). In the integrated hypothesis, an excess release of acetylcholine is the key concept so measurement of acetylcholine at the trigger point is important; unfortunately, this measurement was not made. We should note that trigger points develop not only in the myofascial tissues but also in ligaments, periosteum, and other tissues. The new integrated hypothesis of trigger point formation could not offer a rational explanation for the development of these non-myofascial trigger points that frequently are detected in patients with muscle pain syndromes.

In human subjects, repeated eccentric contractions induce delayed onset muscle soreness (DOMS). Muscle soreness develops 2 to 3 days after the exercises. After eccentric exercise of the middle fingers, a palpable band-like structure with a tender spot develops on day 2. The pain threshold of the fascia, measured by electrical stimulation through an insulated needle electrode, is selectively decreased at the sensitive spot. Moreover,

needle insertion at the sensitive spot provokes a specific referred pain pattern that resembles the pattern observed clinically. After careful insertion of a recording electrode at the sensitive spot, a regular low frequency spike discharge can be detected at the depth of the fascia that is simultaneous with a dull pain sensation. Figure 1 shows a brief summary of the features of the experimental model in humans (21). These features of the sensitive spot are quite similar to those of the trigger point. In rabbits, a similar palpable band and electromyography (EMG) activities were detected and continuous administration of indomethacin, a cyclooxygenase inhibitor, suppressed the development of the experimental trigger point after repeated eccentric contraction of the hindlimb (22). These results suggest the participation of the inflammatory process in the development of the trigger point.

Referred pain and muscle pain symptoms

A most impressive fact for MPS patients is that the true source of symptoms such as headache is not in the head. Trigger points in the neck or shoulder produce referred pain that projects to the head; that is, the subjective symptomatic pain is the referred pain originating in the CNS. Kellgren studied experimental referred pain phenomena systematically in humans. Intramuscular injection of hypertonic saline induced specific patterns of referred pain depending on the site of injection (23). The physiological mechanism of referred pain has been well studied in animal experiments. The convergent-projection theory of referred pain is the most popular and is supported by numerous experimental facts. However, experimental referred pain in human subjects develops with a delay of several tens of seconds, which the simple convergent-projection

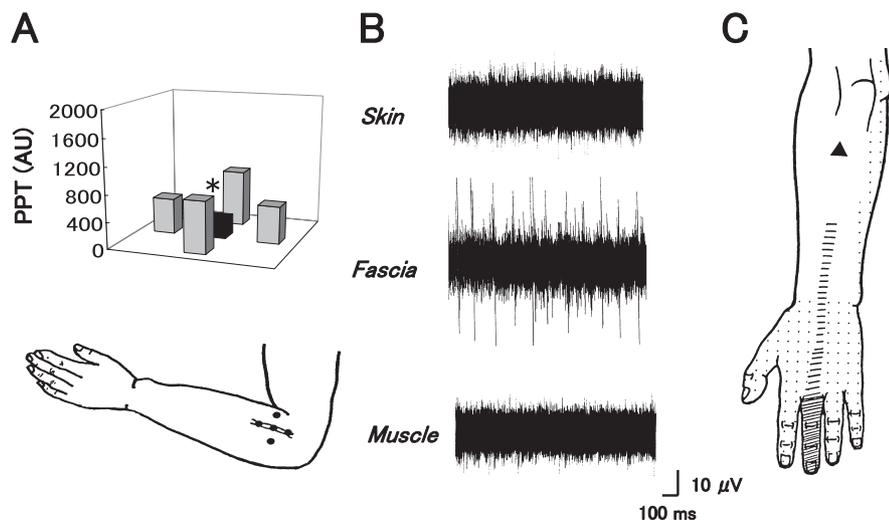


Fig. 1. Experimental trigger points produced by repeated eccentric exercises. Data were recorded on day two after the eccentric exercise. A: Pressure pain threshold (PPT, arbitrary units) measured by pressure algometer. The middle center column with asterisk indicates the experimental trigger point on a palpable band. Columns are 10-mm apart. The lower figure shows the location of the point and the band. B: EMG activities recorded from the skin, fascia, and muscle. Only the fascia is electrically active. C: Referred pain pattern produced by needle insertion to the trigger point in A. (Modified from ref. 21)

theory can not explain. However, Hoheisel et al. demonstrated the role of neural plasticity of spinal convergent neurons in referred pain-like phenomena in myositis rats (24). Intramuscular injection of BK induced a new receptive field or expansion of existing receptive fields in convergent neurons. The changes in the receptive fields might be the result of plastic changes of synaptic transmission mediated by various neurotransmitters. NMDA receptors are a possible candidate for such plastic synaptic changes related to the referred muscle pain.

Possible role of polymodal receptors in acupuncture and moxibustion

The PMRs are thought to be a part of the modes of action of acupuncture and moxibustion because they can be activated by both thermal (moxibustion) and mechanical (acupuncture) stimuli, and they are responsive to chemical substances such as BK. The PMRs have a relatively low threshold and wide-dynamic response range, and they are easily sensitized. Their thresholds are decreased and response magnitudes increased by chemical substances such as PGs, histamine, and BK.

The PMRs have effector functions. They can release neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), somatostatin (STT), and vasoactive intestinal polypeptide (VIP) from their receptor terminals, and these neuropeptides induce inflammatory responses through receptors in blood vessels. It is well known that acupuncture and moxibustion stimulations provoke flare and wheal responses around the site of stimulation (9). The flare (vasodilatation) and wheal (extravasation) are the result of antidromic activation of capsaicin-sensitive thin afferent fibers (25), and antidromic electrical activation of an identified PMR unit

produces a spot-like blue dye extravasation in its receptive field (26). These findings suggest that local inflammatory responses such as flare and wheal induced by acupuncture and moxibustion stimulations might be the results of release of neuropeptides due to the antidromic excitation of the PMR as an axon reflex.

We have proposed a working hypothesis for the peripheral mechanisms of acupuncture and moxibustion (16). Table 1 summarizes the relations among the characteristics of the PMRs, acupuncture and moxibustion stimulation, and the nature of acupuncture points. The PMRs are activated by both acupuncture and moxibustion, and a major functional feature of acupuncture points is tenderness. Sensitization of the PMRs is an important clue. Thus, the existence of sensitized PMRs in the acupuncture/trigger points may provide the major functional basis for understanding the clinical significance of acupuncture points in both acupuncture and moxibustion treatments. The morphological characteristics of acupuncture points are also in agreement with those of the PMRs.

The concept of the meridian system has been considered as an essential theoretical basis of acupuncture and moxibustion therapy; however, no clear evidence for meridians has been found except for the sensory phenomenon of propagated sensation along channels. This meridian phenomenon seems to be a sensory event in the CNS, and it is similar to the specific referred pain pattern elicited by trigger point stimulation (27).

Molecular basis of the functions of the polymodal receptors

Recently, the molecular basis of PMR function has been clarified by a series of investigations of the

Table 1. Similarities among the polymodal receptors, acupuncture and moxibustion stimulations, and acupuncture points

	Polymodal receptors	Acupuncture and moxibustion	Acupuncture points
Sensory modality	A kind of nociceptor (WDR)	Noxious stimuli, but not always painful	
Responsiveness	Responsive to mechanical, thermal, and chemical stimuli	Acupuncture (mechanical + chemical), moxibustion (thermal + chemical)	
Sensitization	Sensitization by various chemicals	Produce various sensitizing substances following minor injury	Sensitized nociceptors are the possible functional characteristic
Sensory phenomena	Evoke deep dull pain sensation	Evoke <i>de-qi</i> sensation	Sensitive spots to acupuncture and moxibustion
Axon reflex	Induce flare and wheal reaction	Induce flare and wheal reaction	
Morphology	Free nerve endings		No particular morphological structures
Distribution	Distribute to whole body	Whole body surface is the target	Distribute to whole body

capsaicin receptor. Numerous reports have demonstrated that various sensory receptors and channels co-exist on the same membrane of a nociceptor (28). Pain-related chemical substances such as BK, histamine, capsaicin, ATP, H ion, STT, NK, and opioids have their own receptors on the same axon terminal and they interact with each other. The structure of the capsaicin receptor is identical to the TRP (transient receptor potential) receptor subtype already known in a fly (*Drosophila*). Among the members of the TRP-receptor family, TRPV1 has multiple responsiveness to chemicals (capsaicin and proton ion) and temperatures over 43°C. TRPV1 receptors are ion channel receptors and are affected by the activation of G-protein mediated metabolic receptors for BK and histamine (29); BK and histamine are also known as potent chemical stimulants and sensitizing substances of the PMR (9). The source of mechanical sensitivity of the PMRs might be an acid-sensing ion channel (ASIC), or tetrodotoxin (TTX)-resistant sodium channels; however, there is no direct evidence that mechano-sensitive ion channels specifically exist in the PMRs. Recently, a role for the Nav1.8 channel in mechano-sensitivity of the C fiber nociceptors was demonstrated (30). Thus, the TRPV1 receptor can provide important clues for understanding the signal transduction and sensitizing mechanisms of the PMRs. Further investigations are required to clarify the molecular mechanisms of acupuncture and moxibustion stimulations.

Analgesic effects produced by TENS, acupuncture, and moxibustion

Activation of the myelinated thick afferent fibers induces an analgesic effect that can be explained by the gate control theory (5) and can be implemented clinically as TENS (6). In the early investigations of acupuncture analgesia, numerous experiments were performed based on the gate control theory that demonstrated the important role of thick afferent fibers (A-beta fibers). It is true that electrical activation of thick afferent fibers through a pair of acupuncture needles induces analgesic effects in humans and experimental animals. Regarding the *de-qi* sensation, microneurogram studies confirmed that the numb sensation was provoked by activation of A-beta fibers and that there are thick nerve bundles under the acupuncture points. Suppression of the jaw opening reflex (JOR), a kind of nociceptive reflex, was related to the amplitude of the A-beta component in the compound action potential (31). These results suggest a role for thick fibers for the development of analgesia; however, the most important issue to clarify is the mechanism of acupuncture and moxibus-

tion. The participation of thick afferent fibers in the EAA mechanism is not the fundamental one underlying acupuncture and moxibustion action because these fibers can not respond to moxibustion stimulation (See Table 1).

Analgesia induced by selective activation of thin afferent fibers and PMRs

Selective activation of A-delta fibers in peripheral nerves with triangular stimulus pulses and electroacupuncture at low frequency (5 Hz) produced a significant suppression of the JOR in rats, whereas maximal excitation of A-beta fibers with square pulses had no effects at 5 Hz (32). This result clearly indicates that the inhibitory effects of A-delta afferent fibers, instead of A-beta fibers, are involved in EA stimulation at low frequency. However, BK is a potent chemical stimulant for the PMR. Figure 2 shows the analgesic effects of intramuscular injection of BK and of thermal stimulation using the JOR as an indicator. Intramuscular injection of BK and thermal stimulation applied to the fascia clearly suppressed the JOR elicited by tooth pulp stimulation, and the time-courses and degrees of naloxone reversibility were quite similar for both conditioning stimuli (9). These observations further support the hypothesis that BK- and heat-sensitive receptors, presumably the PMR, provide peripheral inputs for the activation of endogenous pain inhibitory systems.

Topical application of capsaicin on the nerve trunk selectively abolished conduction in peptidergic thin afferent fibers but did not affect the sympathetic efferent. Furthermore, the conduction of fibers identified with C-PMRs was blocked by capsaicin but that of C-warm fibers was not affected (33). Inspired by the preceding evidence, the participation of PMRs in acupuncture action was examined using topical capsaicin application to the peripheral nerve trunk. Okada et al. clearly demonstrated that manual acupuncture to the hind paw produces a clear suppression of the JOR, but a similar procedure with the capsaicin-treated side has almost no effect. Immersion of the hind paw of the control side in a hot water bath also suppresses the JOR, but immersion of the capsaicin-treated side has no effect (34). These results show that the capsaicin-sensitive thin afferents participate in the peripheral mechanisms of acupuncture action.

Similarity of diffuse noxious inhibitory controls to acupuncture analgesia

Diffuse noxious inhibitory controls (DNICs) refer to inhibition of neural activities of the convergent neurons

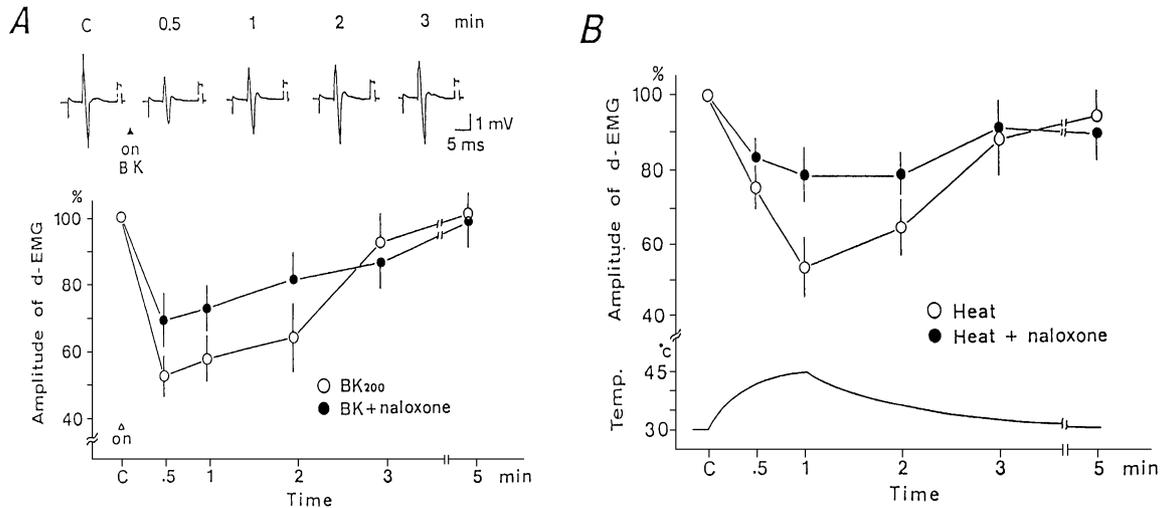


Fig. 2. Partial naloxone-reversible suppression of the jaw opening reflex (JOR) by chemical and thermal stimulation. Similar rapid suppressions of JOR are induced by both bradykinin (BK) injection (A) and heat stimulation (B) applied to the muscle or fascia. Pre-administration of naloxone (1.0 mg/kg, i.p.) partially antagonizes the suppressive effects of both chemical and thermal stimuli. (Modified from ref. 9 with permission from Elsevier ©1996)

in the spinal or medullary dorsal horn by noxious stimuli applied to remote areas of the whole body. DNIC was first reported in rats (35) and is considered to be a neural mechanism of counter-irritation, whereby a noxious input suppresses pain transmission. Bing et al. clearly demonstrated that manual acupuncture to the *Zusanli* (ST36) induced DNIC-like suppression as effectively as hot water immersion, and both suppressions were partially antagonized by naloxone (36). The close correspondence between acupuncture analgesia (AA) and DNIC was confirmed independently by Hashimoto et al. (37) and by Murase and Kawakita (38).

Le Bar's group proposed a role for the subnucleus reticularis medulla (SRD) in the central mechanisms of DNIC (39) and in the descending inhibitory mechanisms (40). Sumiya and Kawakita demonstrated the role of the nucleus submedius (Sm) in the DNIC-like suppression of the viscerosomatic reflex elicited by colorectal distension in anesthetized rats. MA to the cheek or limb suppressed the reflex activities; and reflex inhibition was completely abolished by focal injection of lidocaine into bilateral Sm nuclei, whereas saline injection had no effect (41). To clarify the central mechanisms of DNIC, further investigations are required; however, there might be a common participation of the endogenous pain inhibitory systems and those of acupuncture analgesia. More detailed central mechanisms will be introduced in the next section.

Activation of thin afferent fibers (A-delta and C fibers) is required in the development of DNIC. DNIC is provoked by a noxious pinch, immersion into a hot water

bath, or injection of analgesic substances into muscle (42). Therefore, afferent inputs for DNIC are derived from a nociceptor responsive to mechanical, thermal, and chemical stimuli; and these receptors are distributed through the skin, muscle, and viscera of the entire body. These characteristics of afferent inputs are nearly the same as those of PMRs described in the previous section.

Role of endogenous opioid peptides in electroacupuncture analgesia

Endogenous opioid peptides (EOPs) are considered major candidates for a role in acupuncture action because numerous investigations have clearly demonstrated that EAA is antagonized by the opioid receptor antagonist naloxone (43). An increase of EOPs in the plasma or the cerebrospinal fluid (CSF) following EAA was observed in humans (44). Released enkephalins are rapidly degraded by carboxypeptidase and enkephalinase. Kitade and colleagues demonstrated the blockade of enkephalinase by administration of D-phenylalanine enhanced naloxone-reversible EAA (45).

EAA was significantly attenuated by microinjection of antibodies of β -endorphin and enkephalin into the periaqueductal gray (PAG) matter (46). EAA was suppressed by intrathecal injection of the antibodies to enkephalin or dynorphin but not to β -endorphin (47). Frequency-dependent EOP release by EA was first reported by a Canadian group. Cheng and Pomeranz (48) indicated that EAA could be mediated by endorphin

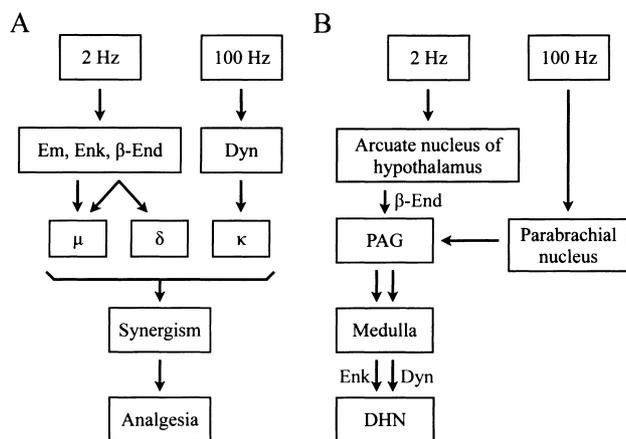


Fig. 3. EAA mediated by different opioids and receptors and their central nervous mechanisms. Two different frequencies of EA (2 Hz and 100 Hz) induce different analgesic actions via four different endogenous opioids and three receptor subtypes (A). The central pathways for analgesic action in the brain (B). Em: endomorphine, Dyn: dynorphin, Enk: enkephalin, β -End: β -endorphin, PAG: periaqueductal grey matter, DHN: dorsal horn neuron. (Modified from ref. 49 with permission from Elsevier ©2003)

and non-endorphin systems. The antagonistic effect of naloxone on EAA was found at low frequency (4 Hz) but not at high frequency (100 Hz) (48). Han's group also demonstrated that different EOPs participated in a frequency-dependent manner in the analgesia induced by conditioning peripheral stimulation. Based on several lines of evidence, Han concluded that low-frequency (2 Hz) EAA is induced by the activation of μ - and δ -opioid receptors via the release of enkephalin, β -endorphin, and endomorphin in supraspinal parts of the CNS; and high-frequency (100 Hz) EAA is caused by activation of κ opioid receptors via release of dynorphin to the spinal cord. Figure 3 is a schematic illustration of Han group's concepts of endogenous opioids and neural substrates of the brain in EAA (49, 50).

Pharmacological bases of tolerance and low- and high-responders in EAA

It is very important to know that prolonged and repeated EAs induce attenuation of EAA, which is referred to as EA tolerance (51). Cholecystinin (CCK) is thought to be the most likely candidate for development of tolerance. Injection of CCK-8 to the cerebral ventricle subarachnoid space significantly attenuates EAA. However, CCK injection does not induce an hyperalgesic effect, and injection of CCK-8 antiserum antagonizes the development of tolerance but does not change the basal pain threshold or enhance EAA in naive rats (52). P77PMC rats have low baseline CCK-8-like

IR in the brain. The analgesic effect induced in these rats by peripheral 100 Hz ES is potent and long lasting, and intraperitoneal injection of CCK-8 suppresses the prolonged analgesic effect (53). The release of various opioids by repeated EA also triggers CCK release in the CNS after which tolerance develops (52).

Another interesting clinical fact is that there are clear individual differences in the response to EAA. Low- and high-responders to EA undoubtedly exist in humans. The responsiveness to EA was systematically investigated in various mouse strains, and clear differences in EAA were observed (54). In the low-responders, a high content of CCK-8 in the PAG was found; and injection of an antisense CCK expression vector to the lateral cerebral ventricle, which decreases the CCK content in the brain, converted a low-responder to a high-responder (55). A newly found peptide, orphanin FQ (OFQ), has also been proposed as a candidate for modulation of EAA. The i.c.v. injection of OFQ antagonized EAA, and blockade of OFQ receptors enhanced EAA and converted low-responders to high-responders (56). These results offer an explanation for the individual variation in EAA and suggest a possibility for new drugs to improve the general efficacy of acupuncture and moxibustion therapies.

Comments on the endogenous opioid hypothesis of acupuncture action

The opioid mediated analgesic mechanism of EA has been established by Han's group; however, there remain several unresolved issues to be considered. Bossut and Mayer clearly demonstrated that EAA could not be antagonized by naltrexone, a selective delta opiate receptor antagonist, in naive rats, whereas a naltrexone-reversible state developed after repeated EA stimulation in the same rat. They also found a potentiation of acupuncture analgesia by naloxone administration. Thus it is difficult to assume that naloxone reversibility is an essential feature of EAA (57).

Sekido et al. reported the involvement of peripheral opioid receptors in EAA. The analgesic effects of EA in carrageenan-treated rats was antagonized significantly by intraplantar injection of naloxone but not by intraperitoneal application (58). This fact points to an analgesic role of peripheral opioid receptors in EA in some pathological conditions, and it also suggests the participation of EOP in the peripheral tissues, including immune cells in EAA.

The current intensity used in EA is a very important parameter for understanding the mechanism of EAA. Han's group used various frequencies of EA, and the current intensity they used seemed to be relatively high.

It is well established that electrical shocks applied to the foot induces analgesic effects, and this phenomenon is named foot-shock-induced analgesia (FSIA). Watkins and Mayer clearly demonstrated that FSIA can be segregated into opioid-mediated and non-opioid mediated analgesia by the parameters of electrical shock and by the sites where foot shock is applied. Intermittent or forepaw foot shock induced naloxone-reversible FSIA, but continuous or hind paw foot shock induced naloxone-independent FSIA. Moreover, the central mechanism of FSIA includes the PAG and descending pathways from the brain stem. The central mechanisms of FSIA are similar to those of DNIC, and the authors consider acupuncture analgesia as a kind of FSIA (59).

Reynolds first reported very impressive evidence that focal electrical stimulation applied to the PAG induces analgesic effects in awake rats (60). After his pioneer work, numerous studies have been conducted that confirmed the analgesic effect induced by focal electrical stimulation of various nuclei in the CNS. The phenomenon was named stimulation produced analgesia (SPA). The effective sites for SPA are located near the central pathway for pain, so common central neural circuits may be utilized by EAA, DNIC, FSIA, and SPA mechanisms. The role of PAG and two major descending inhibitory pathways originating in the brain stem have been clarified. One pathway is serotonin (5-HT) mediated and the other is norepinephrine (NE) mediated, and they originate from the nucleus Raphe magnus (NRM) and locus coeruleus (LC), respectively (61).

Figure 4 summarizes the afferent inputs for activation of various endogenous pain inhibitory systems. There are two different inputs to the CNS that result in different types of analgesia characterized by non-opioid-mediated, segmental, or supraspinal mechanisms. The negative feedback mechanism might be the key concept for understanding analgesic effects induced by various inputs including those produced by acupuncture and

moxibustion.

Effect of acupuncture and moxibustion on the brain rewarding system

Acupuncture and moxibustion have been used for patients with various mental and psychosomatic disorders. Yano et al. demonstrated that acupuncture and moxibustion effectively induce relaxation by affecting the emotional states and evoking pleasant sensations (62). Gentle manipulation of a fine acupuncture needle could produce a subjective comfortable perception, although the neurological mechanism for this has not been determined. Therefore, it is quite interesting to examine whether or not acupuncture and moxibustion can affect reward systems. The pleasantness of acupuncture and moxibustion treatments has been ignored because it has been assumed that these procedures are nociceptive.

In animal experiments, the existence of a reward system was established with a self-stimulation procedure. Rats usually continue pressing a lever for a current pulse applied to certain areas of the CNS. This self-stimulation is assumed to reflect the presence of subjective pleasantness and rewards. The mesolimbic and mesocortical dopamine (DA) systems originate from the ventral tegmental area (VTA) and project widely to regions that include the nucleus accumbens (ACC) and frontal cortex (FC). This pathway, known as the median forebrain bundle, participates in the brain rewarding system. Close concordances between the brain 5-HT systems and somato-psychological stress and influences of 5-HT on the DA system also exist. Therefore the effects of EA on DA and 5-HT contents and their metabolites in the brain rewarding system were examined in conscious rats.

Table 2 summarizes the results obtained in separate experiments conducted by Kato (63) and Yano et al.

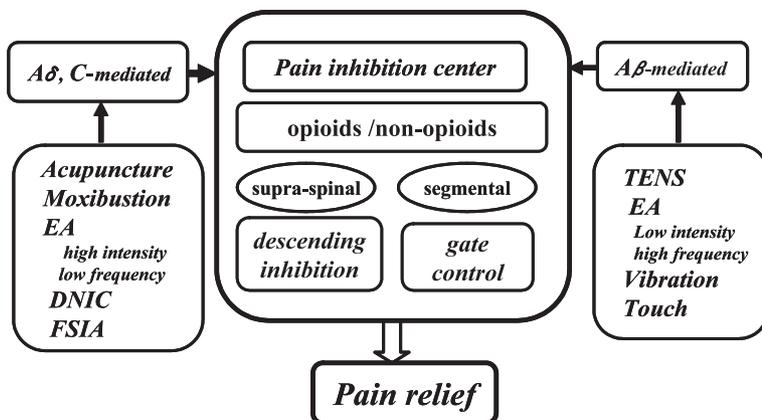


Fig. 4. Schematic illustration of two afferent inputs for the activation of the pain inhibition center. Both thin (A-delta and C fibers) and thick (A-beta fibers) afferents induce analgesic effects via different endogenous pain inhibitory systems. The importance of thick afferent receptors such as the polymodal receptors in acupuncture and moxibustion action should be noted (see text for in details). EA: electroacupuncture; DNIC: diffuse noxious inhibitory controls; FSIA: foot shock-induced analgesia; TENS: transcutaneous electrical nerve stimulation.

Table 2. Effects of electroacupuncture on DA and 5-HT in the brain reward systems

		FC	ACC	C/P	V/S	DRN	LH	HP	AMY
DA	Stress	n.s.	↓	↓	n.s.	↑	↓	n.s.	n.s.
	Stress + L-EA (ST36)	n.s.	↑	↑	n.s.	↓	↑	n.s.	↓
	Stress + H-EA (ST36)	n.s.	↑	n.s.	n.s.	↓	n.s.	n.s.	↓
	Stress + L-EA (BL23)	n.s.	↑	↑	n.s.	n.s.	↑	n.s.	n.s.
	Stress + H-EA (BL23)	n.s.	n.s.	n.s.	n.s.	↓	↑	n.s.	↓
5-HT	Stress	↓	↓	↓	n.s.	↑	↓	n.s.	n.s.
	Stress + L-EA (ST36)	↑	↑	↑	n.s.	↓	↑	n.s.	n.s.
	Stress + H-EA (ST36)	n.s.	↑	↑	n.s.	n.s.	↑	n.s.	n.s.
	Stress + L-EA (BL23)	↑	↑	n.s.	n.s.	n.s.	↑	n.s.	n.s.
	Stress + H-EA (BL23)	n.s.							

FC: prefrontal cortex, ACC: nucleus accumbens, C/P: caudate and putamen, V/S: ventral tegmental area and substantia nigra, DRN: dorsal raphe nucleus, LH: lateral hypothalamus, HP: hippocampus, AMY: amygdala, L-EA: low-frequency electroacupuncture, H-EA: high-frequency electroacupuncture.

(64). The rats underwent low- (1 Hz) or high- (100 Hz) frequency EA at lumbar point *Shenshu* (BL23) or hind limb point *Zusanli* (ST36) during restraining stress. The rats with restraint stress alone had a significant decrease of DA in the ACC, C/P, and LH, whereas there was a significant DA increase in the DRN. Similar significant 5-HT content changes and a significant decrease in the FC were detected. In general, EA induced a similar pattern of changes in DA and 5-HT contents. EA increased the DA and 5-HT contents of the ACC, C/P, and LH and decreased the contents of the DRN and amygdala (AMY), although the degree and significance levels are different. Differences in frequency effects on DA were found in the C/P, LH, and FC and on 5-HT in the DRN. Some regional differences of EA effects were also detected (Table 2). Applications of EA under different conditions elicited different effects on brain monoaminergic neurons in the restrained rats, and these changes may have occurred to compensate for changes in the monoamine levels induced by restraint stress.

Effects of moxibustion were also examined with a similar protocol by Fukuda and colleagues (65, 66). The *Baihui* (GV20) point group was added to the ST36 or BL23 groups. DA, 5-HT, and their metabolites (DOPAC, 5-HIAA) were measured in the monoaminergic neurons of rat brain.

Significant changes in DA, 5-HT, and their metabolites were induced by moxibustion at 6 sites (ACC, LH, AMY, BL23 (ACC), and GV20 (ACC)). A single moxibustion treatment to any point did not change DA or 5-HT levels, but the metabolic turnover of DA increased significantly only at BL23. Conversely, moxibustion at ST36 and GV20 resulted in a significant decrease of the 5-HT level and a significant increase of the 5-HIAA/5-HT ratio for ST36. These results

suggest that the metabolic turnover of 5-HT may be accentuated by moxibustion in a reward-related brain area. Moxibustion over consecutive days, especially to peripheral regions, appears most efficient to influence monoamine levels in the ACC.

Murase and colleagues examined the role of the Sm nucleus in ICSS and SPA and found that the same sites in the Sm are both ICSS- and SPA-positive, at least in part (67). These results are quite interesting because the Sm has been considered a pain center in the thalamus and a site responsible for the development of DNIC. Close relations between the AA and DNIC have been noted previously, and the ICSS-positive sites are in accord with those of SPA-positive sites, although the latter participation was not complete. The role of pleasant perceptions provoked by acupuncture and moxibustion in the development of analgesic and other therapeutic effects is an important issue to examine, but as yet, there have been no such investigations.

Effects of acupuncture on circulation in muscle

Improvement of blood flow has been considered one of the basic mechanisms of acupuncture and moxibustion action. The vicious cycle originating with a strained muscle contraction has been widely accepted as the cause of muscle pain, and the accumulation of various algogenic or sensitizing substances produced by muscle contraction under ischemic conditions is considered the direct cause. Increased blood flow caused by acupuncture and moxibustion may flush out the algogenic or sensitizing substances and induce pain relief. There have been several reports suggesting that acupuncture increases local and remote muscle blood flow (MBF) in human subjects (68, 69). However, the precise mecha-

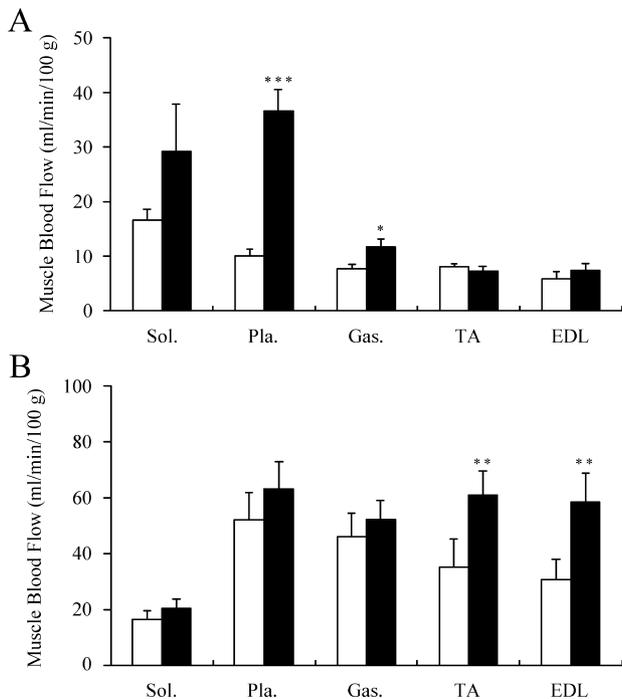


Fig. 5. Increase of muscle blood flow in hindlimb induced by manual acupuncture in rats. Sparrow pecking technique (MA) to the hindlimb increases blood flow only of muscles where an acupuncture needle was inserted. A: Acupuncture to the Sol., Pla., or Gas. muscle induces a significant increase of muscle blood flow (MBF), although MBF to the Sol. is not increased. B: Acupuncture to the TA or EDL induces a significant increase of MBF in the muscle stimulated, but not in the Sol, Pla. or Gas. *** $P < 0.001$ vs control, ** $P < 0.01$ vs control, * $P < 0.05$ vs control. Data is shown as the mean \pm S.E.M. Sol., soleus muscle; Pla., plantaris muscle; Gas., gastrocnemius muscle; TA, tibial anterior muscle; EDL, extensor digitorum longus muscle. (Modified from ref. 70 with permission)

nism of the effects of acupuncture and moxibustion on the improvement of muscle circulation is unclear because the majority of investigations measured the MBF by indirect methods.

Shinbara demonstrated with a radiolabeled microsphere technique that a significant increase of MBF by MA appeared only in muscles in which a needle was inserted. Figure 5 shows the increase of MBF obtained only in the muscle where MA was applied (70). Tsuru also examined the effects of MA on blood flow in rats in various tissues, including muscle, using colored microspheres, and he found increases of MBF at the needling points (71). Sato et al., using a laser Doppler flowmeter, found that repetitive antidromic electrical stimulation of unmyelinated C fibers in dorsal roots increased the ipsilateral biceps femoral MBF in rats, and they determined that the increase in MBF was independent of the mean arterial blood pressure (MAP) (72). These facts suggest that the increase in MBF caused by MA is mediated mainly by an axon reflex in

the muscle.

In a radio-labeled microsphere study, Oda et al. examined the effects of EA on MBF after ligation of the vessel and demonstrated a significant increase in MBF only in the muscle surrounding the EA point 3 days after a repetition of EA. Capillary neovascularization induced by EA via a vascular endothelial growth factor (VEGF) might explain this observation because a clear increase of VEGF-positive cells in the vessels was found (73). Based on the results of a denervation study (74), a hypothesis was proposed that accelerated recovery might be caused by improvement of the MBF via a somato-autonomic reflex. Noguchi and colleagues examined the effect of EA to the hind paw on the ipsilateral biceps femoral MBF using the laser Doppler flowmeter, and they found that EA increased the MBF accompanied with an elevation of MAP (75). Then the increase in MBF caused by EA was assumed to result from a reflex MAP elevation via the sympathetic splanchnic nerve.

Effect of acupuncture on blood flow to and regeneration of peripheral nerve

Clinically, acupuncture and moxibustion to the lumbar areas are used to treat for pain and numbness of the lower limbs. A significant increase in the blood flow (NBF) to the sciatic nerve trunk was obtained by MA to a lumbar muscle in rabbits, although the systemic blood pressure (BP) changed only transiently and slightly (76). EA caused an increase of NBF to the lumbar skin accompanied by an arterial blood pressure elevation (77). However, Inoue et al. observed that the BP independently increased NBF by remote EA (78). NBF is known to be regulated by sympathetic noradrenergic vasoconstrictive fibers, parasympathetic cholinergic vasodilatory fibers, peptidergic afferent fibers, and BP, so that the effect of acupuncture on NBF might be dependent on stimulus conditions such as intensity, frequency, and stimulating site.

Inoue examined the effect of a EA polarity difference on the regeneration of a damaged sciatic nerve. The functional recoveries of the muscles innervated by the injured nerve were accelerated when the cathode was located distal to the lesion site, whereas the opposite arrangement of electrodes induced a recovery delay (79). The present data suggest that EA could be useful as a treatment to promote nerve regeneration, although the mechanism by which EA works is unknown.

Effects of acupuncture on gastrointestinal function

The NIH consensus statement on acupuncture in 1997

has recognized the therapeutic value of acupuncture. Postoperative nausea and vomiting (PONV) and nausea of pregnancy were listed as digestive symptoms that could be treated by acupuncture (3). In Japan, the efficacy of acupuncture and moxibustion on digestive disorders has been well recognized clinically, although scientific research on acupuncture for digestive disorders has begun only recently. In this section, acupuncture and moxibustion effects on digestive function and disorders are reviewed, with a special focus on Japanese work.

Acupuncture actions on gastric acid secretion in humans and animals have been investigated. Noguchi and coworkers found that gastric juice secretion and basal acid output were suppressed with acupuncture to the lower extremities but not to the trunk in humans (80). A marked increase in gastric acid secretion was induced via the vagus nerve by EA to the hind limb in the rat (81). However, Akiyama found that EA has anticholinergic effects and inhibits gastric acid secretion in rats (82), and Jin and colleagues showed that acid secretion suppression by acupuncture was mediated by the release of β -endorphin and STT in dogs (83). It is well known that gastric acid output is strongly influenced by gastrointestinal hormones such as amylase, insulin, gastrins, and secretin. Watsuji et al. examined the effects of EA to the upper extremities or back on the gastrointestinal hormones, and they demonstrated that baseline levels of serum amylase and gastrin were influenced by EA such that this effect might induce changes in gastric acid secretion, although the results were not conclusive (84).

Effects of acupuncture on gastrointestinal motility

In general, electrogastrographs (EGGs) are recorded from surface electrodes non-invasively. This EGG has been used widely to evaluate the effect of acupuncture on gastric motility in humans. Gastric electrical dysrhythmias in the EGG are believed to be associated with gastric motility disorders and are detected in cases of gastric emptying, postoperative nausea and vomiting, motion sickness, anorexia nervosa, functional dyspepsia, irritable bowel syndrome (IBS), and diabetic gastroparesis. Gastric dysrhythmias include tachygastric, bradygastric, arrhythmic, hyperarrhythmic, and bradyarrhythmic (85). The most common acupuncture points for treating gastrointestinal symptoms are the *Neiguan* (PC6) and *Zusanli* points (ST36). Dundee and coworkers reported that acupuncture to PC6 in patients who underwent gynecological surgery had a significant antiemetic effect on postoperative nausea and vomiting (86).

Imai et al. reported that EA at PC6 reduces the severity of symptoms of nausea and normalizes gastric arrhythmia induced by motion sickness in healthy humans (87). It has been demonstrated recently that acupuncture at PC6 reduces the incidence of retching and vomiting induced by vasopressin infusion in conscious dogs (88). These findings suggest that in humans, acupuncture to PC6 suppresses nausea that accompanies gastric arrhythmia mediated by some neuropeptides. However, the detailed mechanism of acupuncture for the improvement of gastric dysrhythmia and nausea is unclear. Imai and colleagues examined the effects of acupuncture on the EGG and analyzed the underlying neurological mechanisms pharmacologically

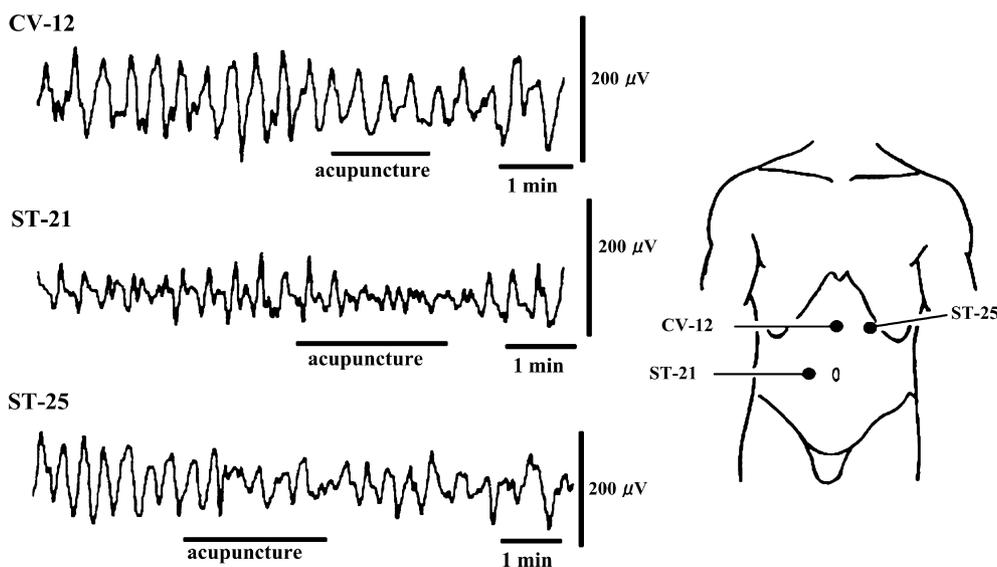


Fig. 6. Effects of abdominal acupuncture on the electrogastrogram (EGG). A decrease in the amplitude of the EGG waves by abdominal acupuncture is clearly demonstrated. Left figure shows three examples of raw EGGs that are suppressed by acupuncture stimulation to acupoints (CV-12, ST-21, ST-25) on abdomen (right figure).

in humans. Decreases in the amplitude of the EGG waves caused by acupuncture were demonstrated, although the degrees of inhibition were not clearly different among the acupuncture points stimulated. Figure 6 shows three examples of raw EGGs that were suppressed by acupuncture (89). Moreover, the changes in the EGG induced by abdominal acupuncture were influenced neither by administration of a vagal stimulator (vagosigmin) or blocker (atropine). These results suggest that the suppressive effects of abdominal acupuncture might be mediated by the sympathetic nervous system via the somato-visceral reflex.

Similar inhibitory gastric responses elicited by abdominal somatic stimulation such as by acupuncture have been shown in anesthetized rats. The gastric motility was often excited via parasympathetic efferent nerves when the limbs were stimulated. The inhibitory gastric response elicited by abdominal acupuncture was mediated by the gastric sympathetic nerves and was not influenced by naloxone, so the response might be mediated via the somato-visceral reflex (90).

To investigate motility in the small intestine, the distance of intra-intestinal movements of carbon particles injected into the stomach was measured in mice. It was found that intestinal motility was accelerated by neostigmine (cholinesterase inhibitor) and reduced by acupuncture and moxibustion and that motility suppression by atropine was accelerated by acupuncture. The effects of acupuncture and moxibustion might be mediated by the sympathetic nervous system (91). In conscious animals with chronically implanted strain gauge transducers, the interdigestive myoelectric complex was increased in frequency during and after EA to the hind limbs (92). Long spike bursts (LSB) associated with colonic motility were recorded by

EMG, and the increase of LSB incidence was apparent in the response to EA at 100 Hz. The i.c.v. infusion of a CCK-A receptor antagonist inhibited the increase of LSB by EA, whereas a CCK-B receptor antagonist had no effect. These findings strongly indicate that EA at 100 Hz induces a release of CCK in the CSF, which accelerates the colonic motility (93).

Effects of acupuncture on urological disorders

Kitakoji and coworkers performed acupuncture at bilateral BL33 acupuncture points (Fig. 7) for overactive bladder; and they demonstrated that urinary incontinence and urgency caused by overactive or unstable bladder, along with improvement in urodynamic measurements such as bladder capacity, were improved (94). In urodynamic measurements of spinal cord-injured patients, acupuncture could be another valuable therapeutic alternative for the treatment of urinary incontinence caused by detrusor hyperreflexia (95). In patients with benign prostatic hyperplasia (BPH), Kitakoji et al. reported that acupuncture stimulation to bilateral BL33 was effective for BPH (stage I) patients (96). Tetsuka evaluated the effect of acupuncture to *Chung-chi* (CV3) on the urine jet phenomenon in twenty healthy humans. Frequency of appearance and maximum velocity of the urine jet increased and duration of the phenomenon was reduced by acupuncture to CV3 (97). The results suggest that acupuncture affects ureter functions and promotes its peristalsis. Tsujimoto examined the effect of a combination therapy of acupuncture and trazodone administration in a patient with psychogenic impotence associated with mild venogenic impotence. Although the administration of trazodone (anti-depressant) alone had no positive effect,

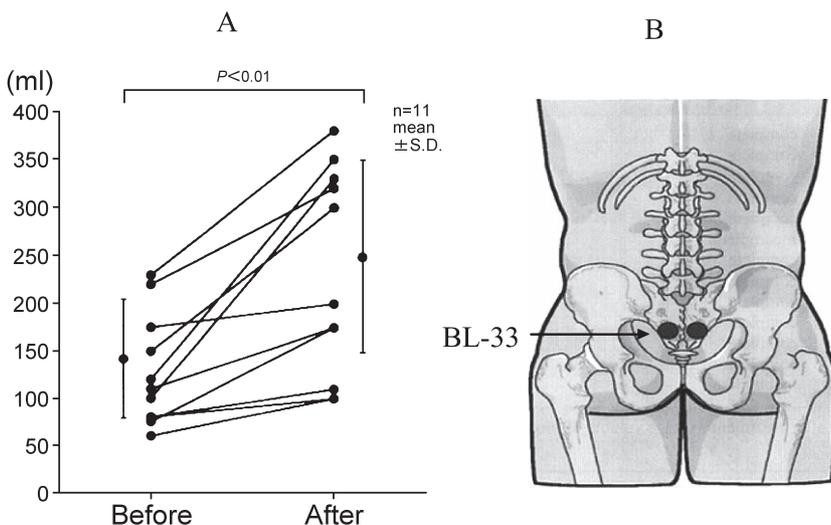


Fig. 7. Effects of acupuncture on maximum bladder capacity in patients with overactive bladder. Acupuncture induces an increase of maximum bladder capacity with statistical significance ($P < 0.01$) (A). Acupuncture points of BL-33 (B). (Modified from ref. 94 with permission)

erectile dysfunction was markedly improved in the patient treated with acupuncture to BL33 (98). Clarifications of detailed mechanisms of acupuncture action are keenly required for the establishment of clinical efficacy.

Summary

Analgesic effects of acupuncture have been well established and the participation of endogenous opioids and their receptors in EAA has been widely recognized. However, the explanation of EAA developed in China seems to be inadequate for explaining acupuncture action on patients suffering pain and other disorders. The general procedures of Japanese style acupuncture and moxibustion are gentle and sometimes induce comfortable sensations, although they are nociceptive in nature. Moreover, careful palpation for detecting tenderness and hardenings under the skin are considered to be extremely important.

The importance of moxibustion should be noted because recent archaeological investigation has demonstrated that the essential role of moxibustion therapy was recognized during establishment of the Chinese meridian theory. The important role of the polymodal receptors, which are responsive to both acupuncture and moxibustion, was discussed in this review. The morphological and functional characteristics of the polymodal receptors can explain the nature of so-called acupuncture points and trigger points. Immediate effects of acupuncture and moxibustion may be explained, at least in part, by the axon reflex via the polymodal receptor. The existence of various endogenous pain inhibitory systems was also pointed out for understanding the immediate effects of acupuncture and moxibustion. Other curative influences of acupuncture and moxibustion on various disorders have been introduced based on research conducted in Japan. Several underlying physiological mechanisms of acupuncture action such as somato-autonomic reflexes were first discovered by Japanese researchers. The unique development of Japanese acupuncture and moxibustion therapies and its contribution to progress in the treatments for various disorders should be emphasized. However, clarification of detailed mechanisms of the therapeutic efficacy of acupuncture and moxibustion, including pharmacological aspects, must be achieved in future studies.

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