The Mechanistic Studies of the Acupuncture and Moxibustion in Taiwan

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ABSTACTS

Traditional Chinese acupuncture has a history of over 2,500 years. It is effective in the treatment of many conditions with few side effects. The best known mechanism is via endogenous opiates and their receptors. In addition to opioids, researchers have focused on the role of central monoamimergic systems. Acupuncture therapy is used not only to relieve pain but also to treat various medical conditions in traditional Chinese medicine (TCM). Some experiments have revealed a relationship between acupuncture and the autonomic nervous system (ANS). Besides, EA can modulate the imbalance between innate and acquired immune systems. This review is focusing on the mechanistic studies of acupuncture that my colleagues and I have performed in Taiwan in recent years. These studies supplement the knowledge of the mechanism of acupuncture.

We found that electroacupuncture (EA) analgesia were closely related to not only the serotonergic neurons but also the adrenergic neurons in the central nervous system. In serotonergic pathway, EA analgesia may be mediated via 5-HT_{1A} and 5-HT_3 receptors. Besides, 5-HT_2 may be involved in high frequency EA analgesia. In adrenergic pathway, both adrenergic α_1 and α_2 receptors were involved in EA analgesia and may be play in the opposite function. In addition, we found that the 2 KHz peripheral stimulation induced an opioid-mediated antinociception in the rat whereas 5 KHz stimulation induced an antinociception which was non-opioid-mediated in nature. From the rats model, a similar degree of analgesic effect was obtained in stimultaneously (S mode) and alternating (A mode). However, tolerance usually developed within five hours in S mode, and was postponed until 10 hours in A mode. We suggest using the alternating mode rather than simultaneous mode for treating chronic pain patients.

We also used electrophysiological recordings to investigate the mechanism of acupuncture. The results revealed that acupuncture stimulation of both Zusanli (ST36) acupoints resulted in a decrease of P300 amplitudes suggested the involvement of the cerebral cortex in acupuncture. No similar changes were observed in the non-acupoint treatment, which have been suggested to be related to so-called acupoint specificity. We also found that EA at 2 Hz depressed the contralateral but not the ipsilateral R2 component of the blink reflex, suggesting that longer pathways, perhaps including the cerebral cortex, may play a role in the physiological mechanisms responsible for the effectiveness of acupuncture.

We also compared the effects of resting cardiopulmonary function under the conditions with or without acupuncture at Zusanli (ST36) and Neiguan (PC6)

acupoints. These results suggested that acupuncture can decrease the resting heart rate and carbon dioxide production, thus lowering the metabolic rate. Ear point pressing may enhance exercise performance and lower lactic acid level following exercise.

Professor Jen-Hwey Chiu has performed several studies to elucidate the mechanism of moxibustion. He found that local somatothermal stimulation inhibited the motility of sphincter of Oddi and internal anal sphincter through nitrergic neural release of nitric oxide. Mild local heat stress upregulated hepatic gene expression of Hsp70 and protected the liver from subsequent ischemia-reperfusion injury. EA and local somatothermal stimulation both attenuated ischemia-reperfusion injury in rat hearts but through different protective mechanisms.

KEYWORDS: Acupuncture, Moxibustion, Mechanistic studies

Traditional Chinese acupuncture has a history of over 2,500 years. Acupuncture has recently increased in popularity and is becoming more widespread throughout some Western countries. It is now known as “complementary medicine”, because it is effective in the treatment of many conditions with fewer side effects compared with other medical procedures, such as surgery or pharmaceuticals.[1]. Furthermore, the WHO has published a guidance describing the efficacy of acupuncture in the cure or relief of 64 different symptoms [2]. For example, acupuncture has been successfully applied in cases of chronic pain, fatigue, nausea, arthritis, and digestive problems.

There are two different strategies used when performing acupuncture therapy; manual acupuncture (MA) and electroacupuncture (EA). EA is a modified form of traditional MA. The advantage of EA is in its combined therapeutic effects of transcutaneous electric nerve stimulation (TENS) and MA. Most studies use EA because EA can be standardized by frequency, voltage, wave form, length, etc. However, although standardization is essential for modern research, some experts do not agree that EA can be a substitution for MA [3].

General Concepts of the Mechanism of Acupuncture

Many studies in animals and humans have demonstrated that acupuncture can cause multiple biological responses [4]. From the neurophysiologic point of view, the mechanical action of needling or its electrical equivalent, i.e. EA, triggers a chain of events that can be understood through controlled experiments. For example, needling may cause receptors to send neural impulses to the spinal cord or act on ascending pathways to the brain, and cause the release of neurotransmitters that subsequently modulate functions in the brain as well as in the periphery [5-7].

The best known mechanism is via endogenous opiates and their receptors. Early works have demonstrated the role that endogenous opiates play in the CNS in acupuncture analgesia. Different kinds of endogenous opiates, such as β-endorphin, enkephalin, endomorphin and dynophin, have been reported to be frequency-dependent factors of EA.

In the 1970s and early 1980s, acupuncture was regarded as a novel pain-killer. Naloxone, an opiate receptor antagonist, was shown to attenuate analgesic actions of acupuncture in humans [8] and mice [9]; the release of a morphine-like substrate in the central nervous system was hypothesized to be a possible mechanism.

In the early 1980s, β-endorphin and enkephalin were purified and it was suggested that they play a role in acupuncture in humans and animals [10-12]. Elevated

levels of endorphin in the cerebrospinal fluid (CSF) were observed in cats after auricular EA. In humans, elevated levels of β-endorphin in the CSF and also of plasma enkephalin were observed after acupuncture. Soon afterwards, the relationship between acupuncture analgesia and different kinds of endogenous opiates was explored in detail. For example, Pomeranz's group was the first to describe the possibility that there are different mechanisms of analgesia when EA is applied with different frequencies [13].

In addition to opioids, researchers have focused on the role of central monoamimergic systems. Particular emphasis is given to serotonin, speculated to be an analgesic neurotransmitter [13]. Evidence suggests that serotonin levels increase in the spinal cord and that its precursor (5-hydroxytryptophan) responds to enhanced analgesia at 2 Hz EA [14]. As more studies are conducted worldwide, theories have been developed regarding serotonin and related descending pain inhibitory pathways [15].

Acupuncture therapy is used not only to relieve pain but also to treat various medical conditions in traditional Chinese medicine (TCM). Some experiments have revealed a relationship between acupuncture and the autonomic nervous system (ANS) [16]. The inflammatory reflex via the ANS could be a possible explanation for acupuncture's diverse therapeutic strategies. Many disorders are thought to be inflammation-related. It is hypothesized that acupuncture can modulate these inflammatory conditions through an inflammatory reflex [17-18]. The hypothalamus is the modulator for both hormonal and neuronal systems. Therefore, the hypothalamus might play a key role in the mechanism of acupuncture [19].

EA can modulate the imbalance between innate and acquired immune systems. EA has been shown to have the ability to adjust the pattern of leukocytes (granulocyte and lymphcyte) in human subjects[20]. Several lines of evidence indicate that this effect is associated with the hypothalamus-pituitary-adrenal axis.

This review is focusing on the mechanistic studies of acupuncture that my colleagues and I have performed in Taiwan in recent years. These studies supplement the knowledge of the mechanism of acupuncture.

Antinociception Produced by 2 and 5 KHz Peripheral Stimulation

The "gate control theory" proposed by Melzack and Wall (1965)[21] claimed that stimulation of the large caliber nerve fiber would suppress the transmission of signals carried by the thin fibers at the spinal dorsal horn neurons. Therefore, peripheral stimulation via electrodes applied to the skin has been a common medical practice under the term "transcutaneous electrical nerve stimulation (TENS)" for health care

and therapeutic purposes, especially for pain control. The electrical parameters of high frequency (100-200 Hz) narrow pulse width (0.1-0.2 ms) and low intensity were chosen which are optimal for stimulating large myelinated nerve fibers, in contrast to the parameters of low frequency and high intensity which are optimal for the stimulation of unmyelinated C fibers.

However, the effects of kilo-Hz electric waves were less reported. We conducted a study in rats to clarify whether electric stimulation over 1000 Hz induced any antinociceptive effect. Tail flick latency (TFL) was taken as the nociceptive index. Electrical stimulation was applied via stainless steel pins inserted into acupoint Zusanli (ST 36) located near the knee joint and Sanyinjiao (SP 6) located near ankle joint on both hind legs. Significant increase of TFL was observed after 2 or 5 KHz stimulation for 10 min, and lasted for the whole stimulation period of 30 min, suggesting that 2 or 5 KHz stimulation induced analgesic effects. Opioid antagonist naloxone (20 mg/kg, sc) produced a 50% blockade of the antinociception induced by 2 kHz but not 5 kHz stimulation. The results suggested the 2 KHz peripheral stimulation induced an opioid-mediated antinociception in the rat whereas 5 KHz stimulation induced an antinociception which was non-opioid in nature [22].

Effects of EA Analgesia on the Central Monoaminergic Neurons：

The Relationship of EA to the Serotonergic Neurons

During the past decades, investigations of the central nervous system mechanisms of EA analgesia have focused on the effect of endorphins. In addition to opioids, particular emphasis is given to serotonin[13]. We attempted to explore the relationship of EA to the serotonergic neurons in the central nervous system. We found that the tail pressure pain thresholds were increased by EA and 5-hydroxytryptophan (5-HTP, a precursor of serotonin) in rats, but decreased by pchlorophenylalanine (PCPA, an inhibitor of serotonin synthesis) and naloxone (a μ-opioid antagonist). The changes in pain threshold produced by EA was reduced by pretreated with PCPA. These results further provided evidence that the EA analgesia has related to activate the serotonergic neurons in central nervous system[23].

The Relationship of EA to the Adrenergic Neurons

Further, we explored the relationship between EA analgesia and other monoaminergic neurons in mice. The writhing responses induced by acetic acid and the pain induced by formalin both were inhibited by EA at 2 Hz, 10 Hz (0.5 msec, 3-5 V). Analgesia induced by EA was potentiated by intracerebroventricular (i.c.v.)

injection of serotonin (5-HT) and norepinephrine (NE), whereas it was attenuated by intraperitoneal administration of synthesis inhibitors of monoamines (p-chloropheny-lalanine, PCPA and α-MT), as well as reserpine, a monoamine depletor. The analgesic effects evoked by EA, 5-HT and NE were inhibited by naloxone. The effects of EA on the monoamine content of the rat brain and spinal cord were determined. The concentrations of NE and 5-HT in the medulla oblongata and the spinal cord were increased by EA. These effects were reversed by naloxone. The study concluded that the effects of EA analgesia were closely related to not only the serotonergic neurons but also the adrenergic neurons in the central nervous system[24].

The Relationships of Different Frequencies of EA Analgesia to Monoaminergic Neurons

In order to understand the relationships of different frequencies of EA analgesia on monoaminergic neurons and opioid receptors, we performed a study using the formalin test in ICR mice. The brain concentrations of endogenous monoamines were determined by HPLC. The evidences suggest that (1) Exogenous 5-HT and NE enhanced the analgesic effect of the different frequencies of EA, especially at 100Hz. (2) The antinociception of EA at different frequencies stimulation (2, 10 and 100Hz) were attenuated by PCPA, and were potentiated by 5-HTP. (3) Prazosin (an adrenergic α_1 receptor antagonist) and clonidine (an adrenergic α_2 receptor agonist) could potentiate the antinociception of different frequencies of EA whereas yohimbine (an adrenergic α_2 receptor antagonist) could reverse 2Hz and 10Hz EA analgesia and potentiate 100Hz EA analgesia. (4) Pindobind-5-HT_{1A} (5-HT_{1A}-directed antagonist) and LY-278584 (5-HT_3 antagonist) could reverse the three different frequencies of EA analgesia and ketanserine (5-HT_2 receptor antagonist) potentiate 100 Hz EA analgesia. The concentrations of brain endogenous monoamines were influenced by different frequencies of EA. From the above results, we suggested that the analgesic effect of EA is related to serotonergic and adrenergic neurons at different frequency stimulation. In serotonergic pathway, EA analgesia may be mediated via 5-HT_{1A} and 5-HT_3 receptors. Besides, 5-HT_2 may be involved in high frequency EA analgesia. In adrenergic pathway, both adrenergic α_1 and adrenergic α_2 receptors were involved in EA analgesia and may be play in the opposite function. [25].

Subtypes of Opioid and Serotonergic Receptors Relating to EA

Further, one study was designed to explore which subtype of opioid and

serotonergic receptors were involved in different frequencies of EA analgesia by the tail-flick test in rats after EA stimulation at Zusanli (ST36). Opioid and serotonergic receptor agonists or antagonists were administered intrathecally. The results showed that naloxone and naltrindole blocked both low and high frequencies of EA analgesia, respectively. The former was more susceptible in low frequency and the latter was susceptible in high frequency of EA. The effects of EA analgesia in three frequencies were attenuated by pretreatment with 5,7-dihydroxytryptamine (5, 7-DHT, analog of 5-HT), implying the serotonergic neuron may participate in the EA analgesia. Furthermore, pindobind-5-HT_{1A} could reverse low and high frequencies of EA analgesia; 8-OH-DPAT (5-HT_{1A} receptor agonist) inhibited the high frequency of EA analgesia but facilitated the low frequency of EAA. Low frequency of EA analgesia was attenuated by ketanserin; 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI, the 5-HT_2 agonist) did not affect the EA analgesia. LY-278584 attenuated the high frequency of EA analgesia and inhibited the EA analgesia. In addition, 2-methyl-5-HT (5-HT_3 receptor agonist) could enhance the EA analgesia[24].

These data suggest that the μ-, δ-opioid receptors and 5-HT_{1A}, 5-HT_2, 5-HT_3 receptors in rat spinal cord are involved in the EA analgesia. The μ- and δ-opioid receptors may play roles mainly in low and high frequency of EA, respectively. However, the exact relationships between EA and 5-HT subtypes on spinal pre- or post-synapse need further studies.

Intermittent-Alternating Mode of Administering EA Stimulation Postpones the Development of EA Tolerance

As above mentioned, EA produced analgesia which is mediated by a variety of central neuro-chemical substances including opioid peptides, and that EA of different electrical frequencies accelerated the release of different types of opioid peptides in the center nervous system. However, no matter which frequency was applied, prolonged EA stimulation for several hours would inevitably lead to a decrease in the analgesic effect, a phenomenon known as “tolerance to EA analgesia,” or “EA tolerance” which hindered the use of “EA anesthesia” during major surgery. Clinical experience has revealed that the effect of EA analgesia can last longer if EA is applied intermittently.

We attempted to change the parameters and mode of stimulation in order to avoid, or at least postpone the development of EA tolerance. EA stimulation was applied to bilateral Zusanli (ST36) and Sanyinjiao (SP6) acupoint in rats, using a simultaneous mode (S mode) to both legs or using an alternating mode (A mode) between the two legs. A similar degree of analgesic effect was obtained in “S” and

“A” modes of stimulation. However, tolerance usually developed within five hours in S mode, and was postponed until 10 hours in A mode. It is therefore suggested to use the alternating mode rather than simultaneous mode for treating chronic pain patients with the benefit of postponing or avoiding EA tolerance without affecting the potency of the EA-induced analgesia[26].

The Cerebral Cortex Play an Important Role in the Physiological Mechanism of Acupuncture

Electrophysiological recordings, such as recordings for evoked potentials, blink reflex and H reflex, were widely used for particular purposes. These signals were stable and the sources could be identified. These signals are suitable to be used to study the mechanism of acupuncture. Professor Ching-Liang Hsieh at China Medical University and I used several electrophysiological recordings to investigate the mechanism of acupuncture.

The Auditory Endogenous Potential, P300

The auditory endogenous potential, P300, is a positive reflection wave with a latency of 300-400 msec. P300 activity originates from multiple cerebral areas[27-30]. It is a reliable method to evaluate recognition of a stimulus by the cerebral cortex. Previous studies have suggested that P300 activity represents cognitive processing, which is evoked by task-relevant stimuli and related to cognitive aspects of discriminating target from non-target stimuli[31-33]. P300 activity has been used widely in the evaluation of neurological and psychological disorders such as denebtia[31-32, 34], schizophrenia[32, 35], multiple sclerosis[36] and thalamic hemorrhage[37].

We therefore investigated the physiological mechanism and response to acupuncture stimulation using the acupoints formula. Scalp-recorded potentials P300 were evoked by auditory stimulation of non-target and target in 13 normal adult volunteers. Latencies and amplitudes were measured. Three assessments were performed in Each subject over a period of at least one week. Each assessment was divided into a control period with no acupuncture stimulation, followed by an acupuncture period and then a post-acupuncture period. Acupuncture needles were inserted into the body as follows: 1) non-acupoint: acupuncture needles were inserted 2 cm lateral to both Zusanli (ST36) acupoints; 2) acupoint: acupuncture needles were inserted into both Zusanli (ST36) acupoints; 3) acupoints formula: acupuncture needles were inserted into both Zusanli (ST36) and Shousanli (LI10) acupoints. Our results showed that both acupoint and acupoints formula assessments resulted in a

significant decrease of P300 amplitudes during the acupuncture and post-acupuncture periods. However, there was significant difference in P300 amplitudes in the non-acupoint assessment during these periods. P300 changes in latencies and amplitudes were not significantly different between the acupoint assessment and the acupoints formula assessment. The observation that acupuncture stimulation of both Zusanli (ST36) acupoints resulted in a decrease of P300 amplitudes suggested the involvement of the cerebral cortex in sensory interaction when simultaneous sensations of the two types are received. No similar changes were observed in the non-acupoint assessment, which have been suggested to be related to so-called acupoint specificity [38].

Sympathetic Skin Response and Somatosensory Evoked Potentials

In order to study the physiological mechanism of acupuncture stimulation, palm recordings of sympathetic skin response (SSR) were evoked by electrical stimulation of the right median nerve on 13 normal adult volunteers. Median nerve evoked short-latency somatosensory evoked potential (SEPs) recordings were taken at least one week after SSR recording. The latencies and amplitudes were calculated. Acupuncture needles were inserted into both Zusanli (ST36) acupoints as follows: 1) manual acupuncture (MA): using fingers to twist the acupuncture needle until so-called Der-Qi was obtained, 2) 2 Hz eletroacupuncture (EA): 2 Hz square-wave electrical pulse were applied between the Zusanli (ST36) needle and the Shangjuxu (ST37) needle bilaterally. The results suggest that acupuncture stimulation of both Zusanli (ST36) acupoints inhibited SSR, which implies that the cerebral cortex contributed at least in part to this inhibition. The stimulation effect of 2Hz EA is stronger than MA [39].

Blink and H Reflex

Either mechanical tapping or electrical stimulation of the supraorbital regions may evoke the blink reflex. The blink reflex has two different components in the orbicularis oculi muscle: (1) an early ipsilateral component and (2) a late bilateral component [40-42]. Several reports have considered the ipsilateral early component of the blink reflex (R1) to be a monosynaptic pontine reflex, with a pathway through the main sensory trigeminal nucleus to the ipsilateral facial nucleus[43-46], while the late bilateral component of the blink reflex (R2) has been considered a multisynaptic reflex, with a pathway passing through the brain stem between the main sensory trigeminal nucleus and the facial nucleus [43, 45-46]. Other studies have demonstrated

that the blink rate may be used to monitor the optimum dosage in drug treatment of Parkinson's disease due to its being mediated by central dopaminergic activity [47-48]. The H reflex can be recorded from the gastrocnemius and soleus muscle in the leg and the flexor carpi radial muscle in the arm by submaximal electrical stimulation of the tibial nerve in the politeal fossa or median nerve at the elbow [49]. The H reflex is thought to originate from a-motorneurons receiving monosynaptic excitation from large Ia afferent fibers [49-50]. It is an effective parameter for evaluating the excitability of a motorneuron pool in the spinal cord [50-54].

We investigated the role of the brain stem and spinal cord in acupuncture. A total of eight healthy adult volunteers were included in the studied. Electrical stimulation of the supraorbital nerve in the supraorbital foramen was used to evoke the blink reflex. Electrical stimulation of the posterior tibial nerve in the right popliteal fossa was used to evoke the H reflex. Electroacupuncture (EA) of 2 Hz was applied to the Zusanli (ST36) acupoint in the right or left leg. The area of the R1 and R2 components of the blink reflex, and the greatest H/M ratio and H-M interval of the H reflex were measured before EA, during EA and at various post-EA periods. These data were analyzed quantitatively by a computerized electromyographic examination system. The results of this study indicate that 2 Hz EA of the Zusanli (ST36) acupoint does not change the R1 component of the blink reflex, and the H/M ratio and the H-M interval of the H reflex, suggesting that 2 Hz EA does not change the monosynaptic reflex in the brain stem and spinal cord in humans. We also found that EA at 2 Hz depressed the contralateral but not the ipsilateral R2 component of the blink reflex, suggesting that longer pathways, perhaps including the cerebral cortex, may play a role in the physiological mechanisms responsible for the effectiveness of acupuncture [55].

Effects of Manual Acupuncture and Transcutaneous Electrical Nerve Stimulation on the H-reflex

We also compared the effect of manual acupuncture (MA) and TENS on the spinal cord using H-reflex recordings. A total of 13 healthy adult volunteers were included. The electrical stimuli were delivered to the posterior tibial nerve transcutaneously at the left popliteal fossa to evoke the soleus H-reflex. MA, 2Hz TENS, 100 Hz TENS, respectively, was applied to the surface of the right first dorsal interosseous muscle exactly at the Hegu acupoint (LI4). Our results indicate that both 2Hz TENS and 100 Hz TENS increased the amplitude of the H-reflex, and that these increases may be retained longer with 100 Hz TENS than with 2 Hz TENS, whereas MA could not increase the amplitude of the H-reflex. MA, TENS at 2 Hz or 100 Hz

didn't change the latencies of the H-reflexes. It is concluded that both 2Hz and 100 Hz TENS increased the amplitude of the H-reflex, suggesting that TENS enhances the excitability of the motoneuron pool in the spinal cord, and 100 Hz TENS has a greater effect than 2Hz TENS, whereas MA was not similar effect to TENS on spinal cord.[56].

Effects of Acupuncture on Exercise Physiology

In addition to analgesia, acupuncture is able to modulate more body functions, such as heart rate and blood pressure, improving the blood flow of coronary arteries, and lower fat and cholesterol levels. It can also be used to improve gas metabolism and pulmonary respiratory function[57-59]. My team compared the effects of resting cardiopulmonary function under the conditions with or without acupuncture at Zusanli (ST36) and Neiguan (PC6) acupoints.

Twelve healthy men volunteers were divided into two groups; one group was needled at Zusnli (ST36) and the other at Neiguan (PC6). The cardiopulmonary functions prior to and after acupuncture treatments were compared. The results revealed that the heart rate decrased when Zusanli (ST36) or Neiguan (PC6) was needled. However, needling at Neiguan (PC6) produced more significant reductions. As to the gaseous metabolism, a decreasing trend was found in both group concerning oxygen consumption (VO_2) and carbon dioxide production (VCO_2), but without statistical significance. These results suggested that acupuncture at Neiguan (PC6) slowed down the resting heat rate, and is more effective than that of Zusanli (ST36) [60].

Further, we compared the effects of Neiguan (PC6) and Zusanli (ST36) with those of non-acupoints on the cardiopulmonary function. Healthy male volunteers were divided into 3 groups with 16 persons in each group. Group 1 was treated with acupuncture at Neiguan (PC6) and Zusanli (ST 36); Group 2 was treated with acupuncture at non-acupoints; and Group 3 was not given any treatment. We found that in the acupuncture groups, resting heart rate and carbon dioxide production were significantly decreased and oxygen consumption was also decreased slightly. This result further supported that acupuncture can decrease the resting heart rate and carbon dioxide production, thus lowering the metabolic rate[61].

Heart Rate Responses and Lactate Level Changes Induced By Pressure Applied to Ear Acupuncture Points

We also investigated whether ear acupuncture affected exercise-induced

heart-rate responses. Twelve healthy male subjects were included. Each subject was applied small objects (seeds, small steel balls etc) taped to ear acupoints. Measurement of 75% VO_2 maximum was performed with and without ear point pressing. We found that (1) ear point pressing significantly increased oxygen consumption at rest and during exercise, but not after exercise. (2) Ear point pressing significantly decreased the heart rate while resting but no significant differences in values were found during and after exercise. (3) Ear point pressing significantly lower the rate of perceived exertion at the tenth and fifteenth minutes, but not significantly at the fifth minute of exercise. These results indicated that ear point pressing may enhance exercise performance by virtue of its beneficial effects on physiological responses [62].

Further, we investigated the effects of ear acupressure on exercise-induced lactic acid levels. Twelve volunteers were included in the study. A significant difference in lactic acid levels was found at 5 and 30 minutes post exercise between the pressed and non-pressed ear point experiments. The results suggested that ear point pressing is effective in lowering lactic acid following exercise.

The Mechanism of Moxibustion

Although the mechanism of acupuncture has been extensively explored, the mechanism of moxibustion has less reported. However, moxibustion has long been used to treat some symptoms, such as stomach pain, nausea and dyspepsia according to the classical literature. Professor Jen-Hwey Chiu at National Yang-Ming University, Taiwan has performed several studies to elucidate the mechanism of moxibustion.

Local Somatothermal Stimulation Inhibits the Motility of Sphincter of Oddi and Internal Anal Sphincter through Nitrergic Neural Release of Nitric Oxide

Nitric oxide (NO) has been known as a biologic substance functioning in signal transduction and in killing victim cells[63-64]. NO also plays a role in the gastrointestinal system and act as a neurotransmitter in nonadrenergic, noncholinergic (or "nitrergic") neurons of the peripheral nervous system[63, 65-66].

To examine whether and how local somatothermal stimulation inhibited the function of the sphincter of Oddi (SO) in humans and in animals with different types of SO, the activity of SO in anesthetized cats and rabbits was measured by using continuously perfused open-tip manometric methods. Local somatothermal stimulation was achieved by applying an electroheating rod 0.5 cm away from the skin area near the right subcostal region. The results revealed that the local

heat-induced SO relaxation was not inhibited by pretreatment with atropine, propranolol, phentolamine or anti-cholecystokinin-octapeptide, but was almost completely blocked by infiltration of local anesthetics. Pretreatment with a nitric oxide synthesis inhibitor also blocked the relaxation, which was reversed by pretreatment with L-arginine, but not by D-arginine. The inhibition of SO motility by local heat in rabbits was also blocked by pretreatment with L-NAME, and this blockade was reversed by L-arginine. Application of local heat on patients demonstrated obvious inhibitory SO responses. These observations concluded that local somatothermal stimulation inhibited the SO motility in animals with different types of SO through the activation of heat-sensitive neural release of nitric oxide. [67].

Further, a study was performed to examine whether and how local somatothermal stimulation inhibited the function of the internal anal sphincter by stimulating nitric oxide release via nitrergic neurons and to elucidate the possible mechanism. Local somatothermal stimulation was achieved by applying an electroheating rod 1 cm away from the skin area at the right popliteal region. The responses were further manipulated by pretreating the rabbits with agonists or antagonists linked to nitric oxide synthesis.

Similarly, the results revealed that local somatothermal stimulation inhibitedinternal anal sphincter motility through the activation of nonadrenergic noncholinergic neural release of nitric oxide [68].

Preconditioning Somatothermal Stimulation on Right Seventh Intercostal Nerve Territory Increases Hepatic Heat Shock Protein 70 and Protects the Liver from Ischemia-Reperfusion Injury in Rats

Hyperthermic preconditioning has been reported to attenuate the heat-induced cellular response to a subsequent severe heat challenge [69-70]. One study was designed to test the hypotheses that hepatic heat shock protein 70 (Hsp70) could be induced by local somatothermal stimulation on right seventh intercostal nerve territory and that preconditioning the rats with local somatothermal stimulation protected the liver from subsequent ischemia-reperfusion injury. The results showed that hepatic gene expression of Hsp70 was upregulated in rats treated with local somatothermal stimulation. When animals were preconditioned with local somatothermal stimulation and followed by subsequent ischemia-reperfusion injury of the liver, there were significant decreases in liver enzymes (ALT/AST) and malondialdehyde (MDA) formation in rats pretreated with one dose of local somatothermal stimulation as compared with those not treated with local somatothermal stimulation or treated with three doses of local somatothermal stimulation. The study concluded that mild local

heat stress (one dose) on right seventh intercostal nerve territory upregulated hepatic gene expression of Hsp70 and protected the liver from subsequent ischemia-reperfusion injury. Therefore, local somatothermal stimulation might provide an easily applicable method for those patients facing ischemia-reperfusion challenge of the liver [71].

Proteomic Analysis Finds Different Myocardial Protective Mechanisms for Median Nerve Stimulation by Electroacupuncture and by Local Somatothermal Stimulation

It is reported that ischemia-reperfusion injury of the heart can be attenuated by application of median nerve stimulation (MNS) through either EA or local somatothermal stimulation[71]. One study was performed in rats to investigate the differences of myocardial protein expression between MNS by EA and by local somatothermal stimulation. The results showed that either MNS by EA followed by a 30-min rest period or by 3 doses of local somatothermal stimulation had cardioprotective effect against ischemia-reperfusion injury. However, the myocardial protein expression profiles are quite different between the EA and the local somatothermal stimulation groups. The study revealed that MNS by EA and by local somatothermal stimulation attenuated ischemia-reperfusion injury in rat hearts through different protective mechanisms and that local somatothermal stimulation might provide an alternative treatment strategy for ischemic heart disease [72].

Conclusion

This review is focusing on the mechanistic studies of acupuncture that my colleagues and I have performed in Taiwan in recent years. These studies supplement the knowledge of the mechanism of acupuncture.

We found that electroacupuncture (EA) analgesia were closely related to not only the serotonergic neurons but also the adrenergic neurons in the central nervous system. In serotonergic pathway, EA analgesia may be mediated via 5-HT_{1A} and 5-HT_3 receptors. Besides, 5-HT_2 may be involved in high frequency EA analgesia. In adrenergic pathway, both adrenergic α_1 and α_2 receptors were involved in EA analgesia and may be play in the opposite function. In addition, from the observations in rats model, we suggest using the alternating mode rather than simultaneous mode for treating chronic pain patients. We also used electrophysiological recordings to investigate the mechanism of acupuncture. The results reveal cerebral cortex may play a role in the physiological mechanisms responsible for the effectiveness of

acupuncture. We also compared the effects of resting cardiopulmonary function under the conditions with or without acupuncture at Zusanli (ST36) and Neiguan (PC6) acupoints. These results suggested that acupuncture can decrease the resting heart rate and carbon dioxide production, thus lowering the metabolic rate. Ear point pressing may enhance exercise performance and lower lactic acid level following exercise.

Professor Jen-Hwey Chiu has performed several studies to elucidate the mechanism of moxibustion. He found that local somatothermal stimulation inhibited the motility of sphincter of Oddi and internal anal sphincter through nitrergic neural release of nitric oxide. Mild local heat stress upregulated hepatic gene expression of Hsp70 and protected the liver from subsequent ischemia-reperfusion injury. EA and local somatothermal stimulation both attenuated ischemia-reperfusion injury in rat hearts but through different protective mechanisms.

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