Basic Research into Japanese Acupuncture
– Mechanisims of action with acupuncture –

KAIM Editorial Department

Over the years, patients have experienced (and acupuncture providers have observed and recorded) the amelioration of physical pain, improvement in a variety of psychosomatic complaints, and recovery of physical condition that can be provided by acupuncture treatment. What accounts for the success of acupuncture in these situations? A variety of theories have been developed over the last 2000 years, and have been described in the historical context of yin-yang five phase metaphysics, ki-ketsu-sui (ki energy, blood, and body fluids) and zang fu organ theory, and meridian system theory.

These inferences regarding disease-related subjective changes as experienced by patients and noted by treatment providers have been explained in detail from an acupuncture perspective, and placed within the context of yin-yang five phase metaphysics and meridian system theory. Unfortunately, acupuncturists' findings have yet not been adequately described from the perspective of scientific mechanisms of action.

However, beginning in the last half of the 20th century and extending into the 21st century, research has begun into the mechanism of the actions of acupuncture. When acupuncture stimulus is applied to percutaneous and subcutaneous receptors (primarily polymodal receptors), and this stimulus is mediated by the nervous system to act on the mechanism of endogenous analgesia, it raise the endogenous opioid level and also activates the autonomic nervous system, the endocrine system, and the immune system. The result is a variety of physiological changes, including analgesia, recovery of organ function, promotion of local and systemic circulation, and the relaxation of muscular tension.

Within the broad field of research into the efficacy of acupuncture in Japan, we focus in particular on work by Dr. Shinjiro Yamaguchi regarding the effects of blood flow of physical sensory stimului as mediated by the autonomic nervous response. We also provide here an in-depth look at the studies being conducted by Dr. Yukihito Sugawara on acupuncture stimulus and nociceptors.

– Somatosensory stimuli including acupuncture modulate blood flow via the autonomic reflexes –

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Introduction

Somatosensory stimuli including acupuncture elicit reflex autonomic responses that affect functions in the cardiovascular system and other organs (Sato et al., 1997). An analysis of the neural mechanisms of somatically induced autonomic reflex responses (somato-autonomic reflex) is essential in developing a scientific understanding of the mechanism underlying the effects of acupuncture therapy.

This article reviews recent studies performed by Japanese researchers regarding vascular reflex responses induced by somatosensory stimuli including acupuncture.

Characteristics of somato-cardiovascular reflex

There has been great progress in research on cardiovascular responses induced by natural somatic stimuli using anesthetized animals in order to eliminate emotional factors. It has been shown that sympathetic rather than parasympathetic nerves play a major role in somato-cardiovascular reflexes. In somato-cardiovascular responses, the brain stem plays an important role as the reflex center. Although spinal segmental stimulation elicits spinal reflex components, such components are usually depressed by descending inhibitory pathways from the brain under a central nervous system (CNS) intact condition. When anesthetized rats are in a CNS-intact condition, somatic afferent stimulation of limbs is particularly effective in producing cardiovascular responses. Limb somatic afferent fibers seem to have specific synaptic connections to the CNS.

Effects of somatosensory stimuli on cerebral blood flow

Background

Recent studies by Sato and colleagues (Sato and Sato, 1992) have shown that cortical cerebral blood flow is regulated by intracranial nerves. Particularly, excitation of the cholinergic nerve fibers originating in the magnocellular nucleus of the basal forebrain (the nucleus basalis of Meynert; NBM) releases extracellular acetylcholine (Ach) in the cortex, resulting in an increase in cortical blood flow, independent of metabolic vasodilation.

Acupuncture-like stimulation

Uchida et al. (2000) demonstrated the effect of acupuncture-like stimulation for 1 min to various skin areas on cortical blood flow measured using a laser Doppler flowmeter in anesthetized rats. The results clearly showed that the increase in cerebral blood flow, independent of systemic blood pressure, elicited by acupuncture stimulation is a reflex response in which the afferent nerve pathway is composed of somatic groups III and IV afferent nerves, and efferent nerve pathway includes intrinsic cholinergic vasodilators originating in the NBM.

As proven by Hotta et al. (2002), ischemia-induced delayed death of rat cortical neurons can be protected by preventing a blood flow decrease in widespread cortices via NBM-originating vasodilative activation. Therefore, it appears that continuous acupuncture stimulation prevents cerebral infarction though its vasodilative effect in the cerebral cortex.

Effects of somatosensory stimuli on peripheral blood flow

Sympathetic reflex

The effect of electro-acupuncture stimulation (EAS) to a hindpaw (0.1-10 mA, 20 Hz, 30 s) on muscle blood flow measured by laser Doppler flowmetry and on mean arterial pressure (MAP) was investigated by Noguchi et al. (1999). EAS to a hindpaw at a strength sufficient to excite group III and IV afferent fibers, can produce a reflex increase and/or decrease in muscle blood flow. They clarified that two types of responses are induced passively by pressor response via a splanchnic sympathetic activity, and/or directly by an activation of muscle sympathetic nerves.

Are small vessels such as arterioles affected by somatic afferent stimulation including EAS? The authors' group (Takagi et al., 2005) investigated the effects of EAS of the hindpaw and the dorsal Th13-L1 level area on the mesenteric microhemodynamics in anesthetized rats using an intravital microscope system. We observed that the hindpaw EAS evoked intensity-dependent pressor responses and an increase in blood flow velocity, measured by the dual-sensor method developed by the authors, in mesenteric precapillary arterioles, while the dorsal EAS evoked depressor responses and a decrease in blood flow velocity. Occasional but notable reflex vasoconstrictions in the mesenteric terminal arteriole by EAS of both sites were observable on the image under the intravital microscope. These vasoconstrictive responses were not affected by the administration of an alpha-adrenergic blocker. Our study directly demonstrated that hemodynamic changes at the level of precapillary arterioles accompanying EAS either on the hindpaw or the back, mainly depend on the changes of systemic arterial pressure regardless of stimulation current intensities. Moreover, the results in our study suggest some receptors other than alpha-adrenergic receptor might be involved in the mechanism of EAS-induced vasoconstriction in the mesenteric arteriole.

Sato et al. (1996) demonstrated that acupuncture-like simulation induced catecholamine secretion from the adrenal medulla via activation of the adrenal sympathetic nerves in anesthetized rats.

To examine whether such somatically induced catecholamine is effective on microvascular tone, the authors investigated the effects of 10 min (3 mA) of electrical stimulation of the dorsal skin area (Th5-12 level) on the mesenteric arterioles in anesthetized rats using an intravital microscope system (Yamaguchi et al., 2002). Electrical stimulation of the skin for 10 min evoked a decrease in the diameter of arterioles. In the adrenalectomized group, electrical stimulation of the skin for 10 min elicited a slight increase in the diameter (Fig. 1). It is therefore suggested that the constriction of the mesenteric precapillary arterioles induced by the stimulation for 10 min was mediated by humoral adrenaline and noradrenaline released by somato-adrenal medullary reflex.

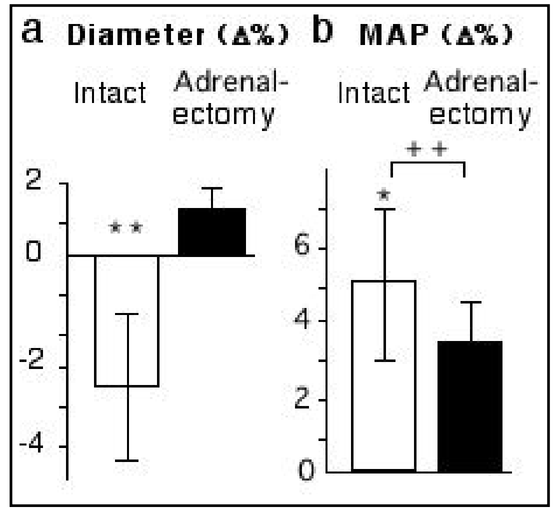

Figure 1: Effects of adrenalectomy on precapillary arteriolar constriction (a) and pressor response (b) induced by electrical stimulation (ES) of the back skin (3 mA, 20 Hz, intermittent, 10 min) in anesthetized rats. The open bar shows the responses to ES in the intact rats. The closed bar shows the responses induced by ES in the bilateral adrenalectomized rats. *p<0.05, **p<0.01; statistical significant is obtained between the pre-stimulus values and the values at 4-5 min (a) and 2-3 min (b) after onset of the stimulus. +p<0.05, ++p<0.01; statistical significance is expressed between responses in two groups. (Modified from Yamaguchi et al. 2002)

Nitric oxide

It is well known that nitric oxide (NO) is a physiologically active substance producing various functions. NO, especially, plays an important role in vasodilation in arterioles.

In the knee joint, blood flow is known to be modulated mainly by sympathetic postganglionic fibers, but recently the release or induction of NO synthesis in response to electrical stimulation has also been suggested. Therefore, direct observation of the microcirculation is needed to further understand the mechanism by which blood flow is regulated by somatic afferent stimulation. The author's group (Loaiza et al., 2002) observed the effects of EAS (5 mA, 0.5 ms, 5 Hz, 30 min) to the vastus medialis muscle on MAP and the knee joint microcirculation using a real-time confocal laser-scanning microscope system.

Significant and persistent increases in arteriolar diameter and MAP, were observed after EAS to the muscle. EAS to the vastus medialis in the presence of N(omega)-nitro-L-arginine methyl ester (L-NAME) produced a strong decrease in diameter of the knee joint arterioles under the baseline with a simultaneous increase in MAP. EAS to the skin did not produce changes in arteriolar diameter while a slight increase in MAP over the baseline occurred after the stimulaitons. EAS to the muscle after neuromuscular blockade did not produce significant changes in diameter, while an increase in MAP was still observed, which suggests that muscle contraction is required to produce vasodilatation (Fig. 2). These responses suggest that a dynamic balance between the autonomic nervous system and the release of NO is the primary mechanism mediating the EAS effects on knee joint microcirculation.

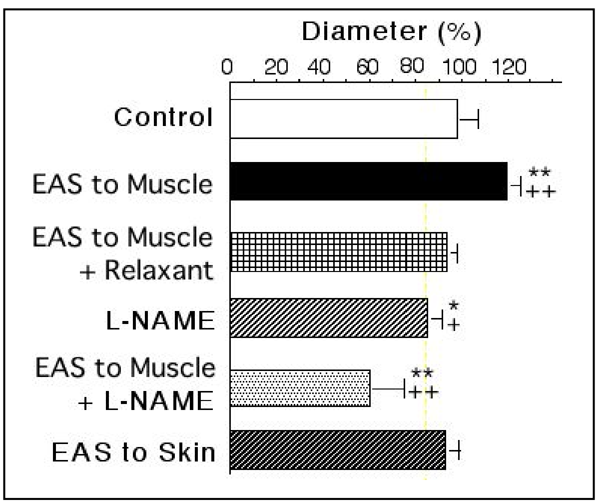

Figure 2: Summarized data on the changes in joint capsule arteriolar diameter in anesthetized rats. The values were registered at 30 min of observation in the control (non-stimulated) and L-NAME group and at the end of the stimulus in the electro-acupuncture stimulation (EAS) to vastus medialis muscle, EAS to the muscle + L-NAME, EAS to the muscle + relaxant and EAS to skin groups. Statistical significance is indicated as *p<0.05, **p<0.01 when compared to the pre-stimulus values, and +p<0.05, ++p<0.01 when compared to the control group. (Modified from Loaiza et al. 2002)

Axon reflex

When an axon reflex is induced by cutaneous stimulation, the excited afferent terminal releases vasodilative substances, such as calcitonin gene-related peptide (CGRP).

The contribution of CGRP to antidromic vasodilation of skeletal muscle blood flow following electrical stimulation of muscle afferent was investigated by Sato and colleagues using anesthetized rats. They concluded that antidromic vasodilation in skeletal muscles following stimulation of unmyelinated C afferents in dorsal roots is independent of systemic blood pressure and is mediated essentially by CGRP. They described that this CGRP-related antidromic vasodilation is probably important in the clinical improvement of skeletal muscle blood flow caused by physical therapy such as acupuncture.

The authors assessed by measurement of two different hemodynamic parameters: muscle blood flow using a laser Doppler flowmeter; and the changes in diameter of the muscle arterioles observed directly using an intravital microscope system in order to examine the effects of electrical stimulation (5 V, 20 Hz, 30 s) to the saphenous nerve on microcirculation of the gracilis muscle in anesthetized rats (Loaiza et al., 2002). We found that ipsilateral nerve ES produced vasodilative responses in the muscle accompanied by increases in muscle blood flow independently of the sympathetic nerve activity. Furthermore, CGRP was found to be directly involved in the reflex neural regulation of the muscle microcirculation, which suggests the participation of an axon reflex mechanism (Fig.3).

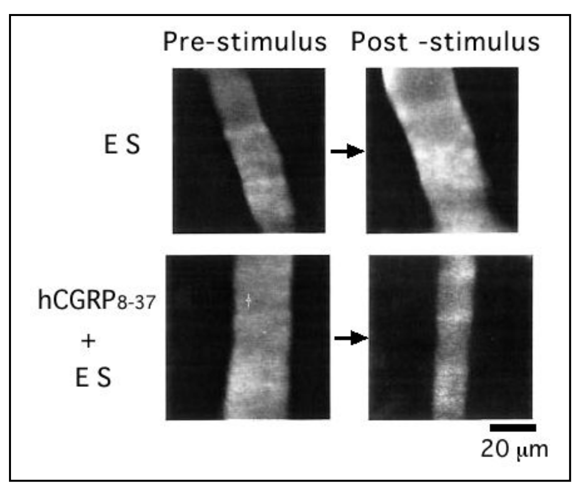

Figure 3: Effect of ipsilateral electrical stimulation (ES) of the saphenous nerve on gracillis muscle arteriolar diameter in the absence and presence of

topical CGRP8-37. Representative photographs of two different arterioles, observed pre- and post-stimulus are illustrated. (Modified from Loaiza et al. 2002)

Conclusions

1. The cerebral blood flow response induced by acupuncture-like stimulation of a forepaw in rats, independent of MAP, is a reflex response whose afferents are group III and IV somatic afferent fibers, and whose efferents are cholinergic fibers originating in the NBM.
2. The somatically induced peripheral circulatory regulation system consists of three types of mechanisms as follows.
   (1) Hemodynamics in the region of interest is affected by systemic circulatory changes induced by the somatic afferent stimulation.
   (2) The observed blood vessels are directly affected by activating the autonomic efferent nerve fibers including nonadrenergic, noncholinergic fiber that can release NO.
   (3) Vasodilative response induced by the CGRP through activating the primary afferent fibers (axon reflex).

These physiological findings may support the effectiveness of acupuncture therapy on patients with circulatory disturbances.

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– Correlation between Nocicepetion and Acupuncture and Moxibustion –

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I. Introduction

Acupuncture and moxibustion therapy is a primitive stimulation therapy during which either needles are inserted into the tissue or moxa is burned on the skin, thereby causing minor damage to the tissue and skin. These stimuli can alleviate pain and elicit various reactions from the autonomous nervous system, but at the same time the stimuli themselves also produce a pain sensation and thus excite nociceptors. In a manner of speaking, this would be like "using pain to kill pain", where a basic negative feedback mechanism can be considered to underlie the induction of the effects brought about by the acupuncture and moxibustion stimulation[1,2,3].

Acupuncture and moxibustion is characterized by stimulation of specific sites called acupoints, but its applications are extremely varied. Although this treatment form cannot easily be defined, the stimulus modalities can be classified as mechanical nociceptive and thermal nociceptive stimuli. In the end these stimuli cause some degree of local tissue lesions, the release of various algesic substances or their relevant modulator substances, or else the production and release of neuropeptides. From this point of view it is necessary to consider this modality to act as a chemical stimulus.

Moreover, these stimuli excite nociceptors, activating endogenous analgesic mechanism[4,5,6,7] and lead to the manifestation of various effects on the autonomous nervous and endocrine systems[6], or else they may also influence the immune system[7] and for this reason acupuncture and moxibustion have been used since ancient times to cure all kinds of complaints and symptoms.

On the other hand, in our research department, with Mr. Kazuhiro Goto as the leading figure, we have employed microneurography for the purpose of studying the correlation between the activity of human nociceptors and pain in order to directly record human peripheral nervous activity. Among cutaneous and deep afferent neuronal activities we recorded the activity of C-fiber thermomechanical nociceptors (synonymous with C-fiber polymodal nociceptor, C-fiber mechanical heat nociceptor: CMH) [8,9,10,11] and A-fiber nociceptors [8,12,13] and thereby investigated the correlation between pain and acupuncture and moxibustion stimulation.

In the present paper the correlation between pain and acupuncture or moxibustion stimulation will be discussed, while adding some of the insights pertaining to the activity of human nociceptors obtained through microneurography.

II. Characteristics and application of microneurography

Peripheral nerve activity in non-sedated humans was recorded using microneurography and systematically researched by the Swedish researcher Hagbarth, Vallbo[14] et al. and in Japan by Honno et al.[15].

This method employs percutaneous unanethetized insertion of tungsten microelectrodes that are isolated with the exception of a few µm at their tip to directly record the potential action of nerves. In this way the correlation between the activities of human skin mechanoreceptors[16], sympathetic nerves of muscles[17], muscle spindles, tendon organs and other proprioceptors on the one hand; and pyramidal muscle activity on the other hand[18]; as well as the nerve activity of afferent C-fibers from the skin and sympathetic activity[19,20,21] etc. were analyzed.

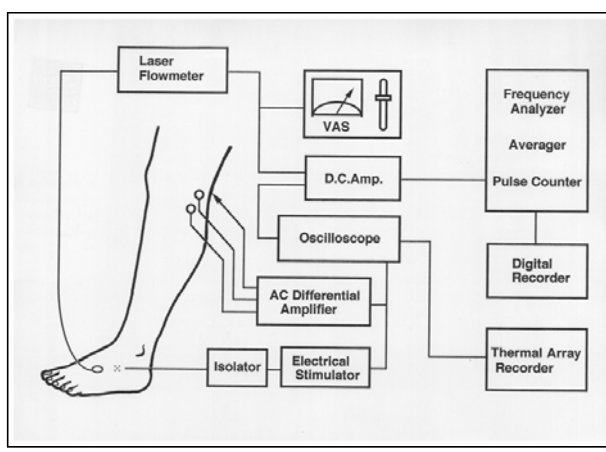

Figure 1

Figure 1 shows a diagram of this method. A tungsten recording microelectrode with an impedance of several MΩ to over ten MΩ is used for the recording of the action potentials, while the indifferent electrode is attached nearby on the skin as a disk-shaped earth electrode. The signals were amplified using a high-impedance type amplifier and a DC amplifier and then observed on the cathode ray tube of an oscilloscope. The data were recorded at all times during the observation.

The electrode was inserted percutaneously above nerve trunks. To determine a suitable location for the insertion of the electrode, the course of the nerve can be confirmed in advance by applying electric stimuli to it. At this time the motor nerve conduction velocity (MCV) or the sensory nerve conduction velocity (SCV) at the site for the insertion was determined by using the evoked wave forms obtained during the measurement as an index to make the approach of the electrode to the nerve still more reliable.

The electrode was then advanced by hand towards the nerve. The occurrence of a transient unusual sensation confirmed that its tip had reached the nerve trunk. Simultaneously, the output of the characteristic nerve activity via a sound monitor was also possible. When the tip of the electrode had reached a muscular branch, a deep, diffuse, dull pain ran through the depth of the muscle; or in case of reaching a dermal branch a transient feeling of superficial numbness occurred.

In this way, the derived action potentials of the nerves are in the beginning action potentials of several units, but through subtle and very careful manipulation of the inserted electrode the discharge of single units or cluster discharge with a very good S/N ratio are isolated. During this process, first the activity of afferent nerve fibers of the relevant peripheral receptive field is probed and then the nerve conduction velocity measured by applying electrical stimulation to this receptive field. Or alternatively, by applying various stimuli (mechanical stimuli, muscle contraction of stretch stimuli, heat stimuli and chemical stimuli) the activity of the particular unit is qualitatively identified. Moreover, regarding the activity of postganglionic sympathetic fibers or similar efferent nervous activities, a variety of load tests of the autonomic nervous systems are performed, or else the origins of nervous activities related to heart rate, breathing or sweating etc. are determined.

In this way, recorded nerve activity, in particular the activity of primary afferent cutaneous nerve terminals, can be analyzed in direct comparison with the intensity of the sensory responses experienced by the subjects. Through stimulus-response analysis it is possible to measure the intensity of the direct subjective sensory responses. Moreover, during research into acupuncture and moxibustion it is not only possible to analyze what kind of primary afferent terminals the acupuncture or moxibustion stimulation produces analgesic effects and elicits various responses of the autonomous nervous system, but it is also considered possible to examine through analysis of the excitation of peripheral receptors in the skin or muscles at the site of acupoints, what kind of peripheral receptors the so-called "de qi phenomenon" are related. Thus, the application of microelectrodes is a very useful tool for research into human peripheral nerve activity within the field of studies pertaining to acupuncture and moxibustion. In the present paper we have focused in particular on acupuncture or moxibustion stimulation induced activity of primary afferent terminals in the skin and discuss the results, adding the insights we have gained.

III. Input system for acupuncture or moxibustion stimuli (correlation to the nociceptor system)

Assuming that acupuncture and moxibustion stimulation in itself produces some minor lesions of the peripheral tissues, in particular in case of needling stimulation, the insertion or mechanical manipulation of the inserted needle(s) may elicit beside the prick pain a peculiar abnormal sensation called "de qi (tokki)". There are a variety of different patterns associated with this de qi sensation, but in any case its characteristics are close to the sensation of pain. Based on these facts, the likelihood of the possibility increases, that the peripheral receptors excited by the acupuncture or moxibustion stimuli are rather nociceptive receptors than non-nociceptive, proprioceptors. These considerations suggest, and based on considerations of the input system through which the acupuncture or moxibustion stimulation acts, that cutaneous and subcutaneous nociceptors are representative for the polymodal nociceptors playing the most important role here.

1) Polymodal nociceptors

Afferent fibers transmitting nociception include C-fibers and A-fibers. On the other hand, polymodal nociceptors are widely distributed throughout the entire body and serve as the most important nociceptors within the input systems of the bodily defense[22].

One property of polymodal nociceptors is, that morphologically they are free nerve endings and widely distributed throughout the body, spreading antennas that pick up abnormal stimuli applied to the body. Moreover, the modality of the stimuli has a low specificity, so that they may react to mechanical stimuli, heat stimuli, or the chemical stimuli provided by endogenous algesic substances. Thus they are characterized by the advantage that they do not distinguish between the nature of the stimuli as long as it is a nociceptive stimulus. Further, the excitability in response to stimuli has a wide range from the non-nociceptive level to the nociceptive level, throughout which these receptors respond strongly and thus cause the body to sensitively react to abnormal stimuli. This means, that these characteristics are marked by a high input sensitivity of the body's warning system, so that they also encode signals caused by abnormal stimuli, even if those stimuli are not necessarily associated with irreversible tissue damage.

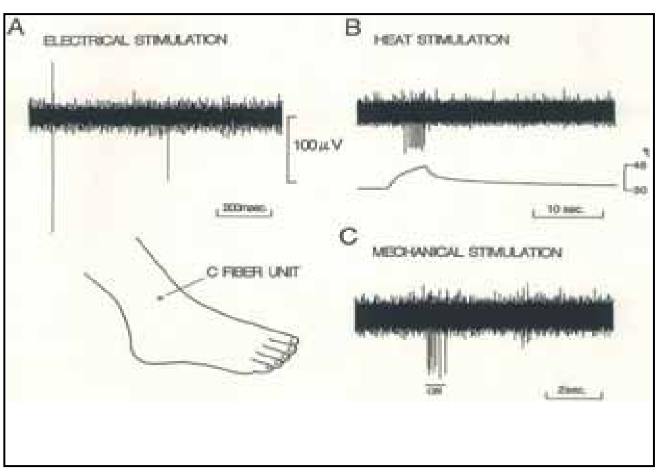

Figure 2

Figure 2 shows the evoked firing of human cutaneous C-fiber thermomechanical nociceptors (CMH) following electrical, mechanical and thermal stimulation[8].

In case of single discharge recordings from CMH, the threshold within the receptive field in response to electrical stimulation is considerably lower than the electrical threshold of C-fibers stimulated via nerve trunks, so that pain sensations are negligible. The threshold for mechanical and heat stimulation has a wide distribution range (Figure 3), so that firing activity is observed even from comparatively low stimulation intensities.

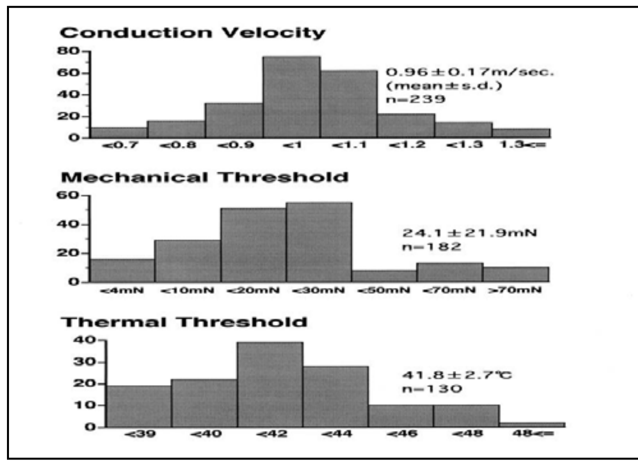

Figure 3

Again, the average temperature in case of thermal stimulation was 41-42°C and the categories corresponding to the subjects subjective sensation of the intensity of the thermal stimulation were at "warm" or "hot" levels. When CMH are in this way classified as nociceptive receptors, the ranges for the individual stimulation types are very wide and one of their characteristics can be said to be their firing activity ranging from non-nociceptive stimulus intensities.

The firing of the CMH increases depending on the intensity of the nociceptive stimuli. Tentatively they encode the intensity of the sensation comparatively accurate and thus enable central discrimination of both localization and intensity[23,24,25,26,27].

For example, when the tentative characteristics of CMH in their response to the stimulus intensity in case of thermal stimulation is examined, an approximate dependency of the firing activity on stimulation intensity is observed (Figure 4).

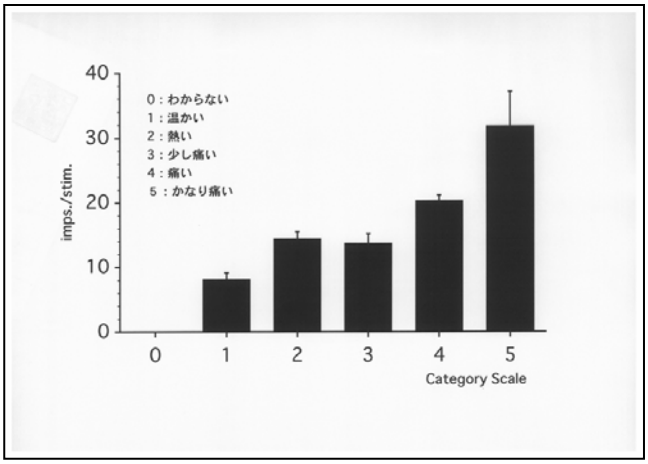

Figure 4

However, in this case the temporal intervals between repetitions become shorter, so that it is influenced by preceding stimuli. In particular, in connection with strong preceding stimulus a low correlation to the firing frequency is observed, characterized by a lower reproducibility of the excitation than from other cutaneous sensory receptors [10,11]. Accordingly, the function of CMHs is to transmit the algesic sensory information, but regarding the intensity of the nociceptive input, the transmission is neither necessarily continuous nor true. The CMH are thus considered to serve mainly the transmission of early information pertaining to conditions potentially harmful to the body.

Moreover, the changes in the tissue induced by the nociceptive stimulus is transmitted and the condition of the tissue conversely modifies the receptors themselves, so that they are considered to fulfill their original purpose as polymodal receptors within the biological defense.

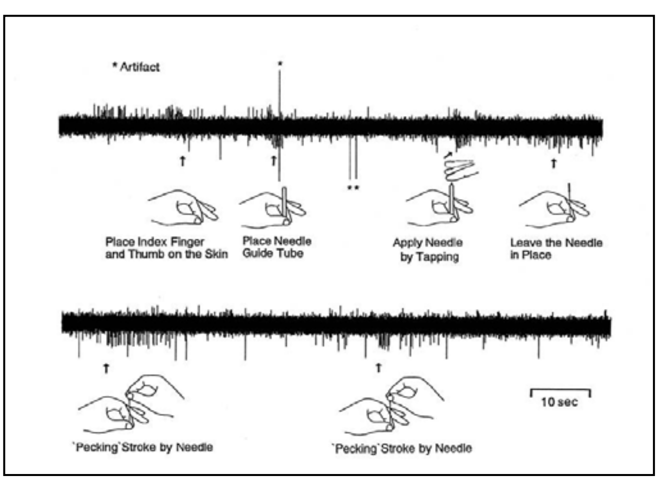

Figure 5

On the other hand, needling stimulation easily excites the CMH (Figure 5). If a series of acupuncture manipulations have been performed within the CMH receptive field, simply erecting the needle tube there after positioning the pressing hand induces firing activity. Next, the performance of needle tapping to insert it through the skin results in a transient, dynamic firing, whereas for the needling technique called thrusting and lifting, where the needle is moved up and down as if in pecking movements, it also induces dynamic firing activity. With this kind of thrusting and lifting stimulation, single unit firing activities show a firing frequency of more than 10 impulses per second, but in most cases the subject does not experience any tingling prick pain.

In spite of the fact that such a series of manipulations induces high frequency CMH firing, it does not cause the subject any pain. Since the acupuncture stimulus itself is a punctuate mechanical stimulus, it is difficult to obtain peripheral or central spatial summation. For example, this indicates that even if the CMH would be firing, it does not necessarily mean that this will lead to the perception of a "de qi" sensation.

Also, thick fibers are simultaneously excited through the pressing hand or movement of the needle, which are considered to be related to pain inhibition, also suggesting a correlation to the manifestation of effects of acupuncture stimulation brought about by retaining the needles, intradermal needles or shallow needling just piercing the skin.

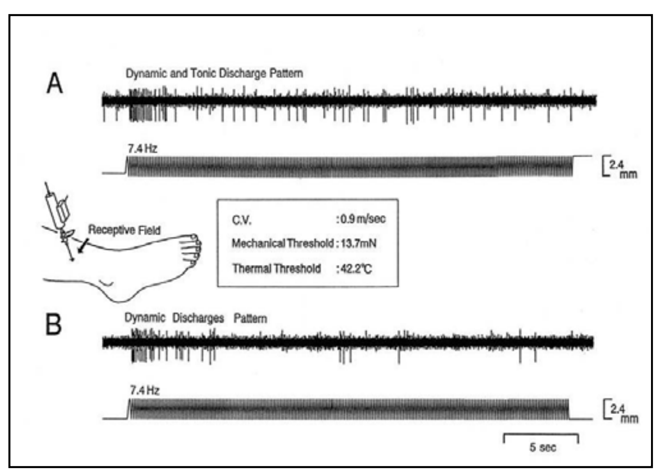

Figure 6

Figure 6 shows the firing activity of CMH when an acupuncture stimulation of constant frequency is applied using a thrusting and lifting stimulation device. Continuous stimulation period was 30 seconds, thrusting and lifting frequency 7.4 Hz and amplitude 2.4 mm; the upper and lower row show the firing activity of the same unit.

The firing pattern shown in the upper row shows a strong dynamic activity during the starting phase of the thrusting and lifting. After that the stimulation frequency was not followed, but rather a static firing activity continued. Moreover, the lower row shows only early phase dynamic firing activity, which is a pattern lacking the static firing components observed during the latter half. With neither of these two patterns did the subject feel any pain, but reported only a sensation of vibration.

These differences in firing pattern, in spite of originating from the same CMH firing activity, are easily influenced by preceding stimuli and are considered to be the manifestation of a fatigue phenomenon. Also, applying acupuncture stimulation frequently results in the development of flares or swelling in the vicinity of the needled site. This is considered to be the result of neurogenic inflammation caused by the excitation of these polymodal nociceptors[1,2,28].

In this respect, attention has been paid to the action of polymodal receptors as effectors, where the excitation of these polymodal receptors serves as retrograde stimulus; while in the manner of axon reflexes from the free nerve endings in the vicinity substance P or CGRP (calcitonin gene-related peptide) and similar neuropeptides are released, hypothetically causing inflammatory reactions like vasodilatation or plasma exudation[29].

On the other hand, moxibustion stimulation induces a high firing frequency of the CMH. Figure 7 shows the CMH firing activity induced when in the vicinity of a mechanically stimulated receptive field with the relevant sensitivity moxibustion is repeatedly performed in a different receptive field[30].

Direct moxibustion with small cones of moxa with a temperature of 60 - 70°C produced a strong nociceptive thermal stimulus and cause a local burn, but CMH firing activity is observed even after 3 repeated applications. This means that the receptive field at the site of the moxa treatment has not sustained destructive lesions by the moxibustion stimulus.

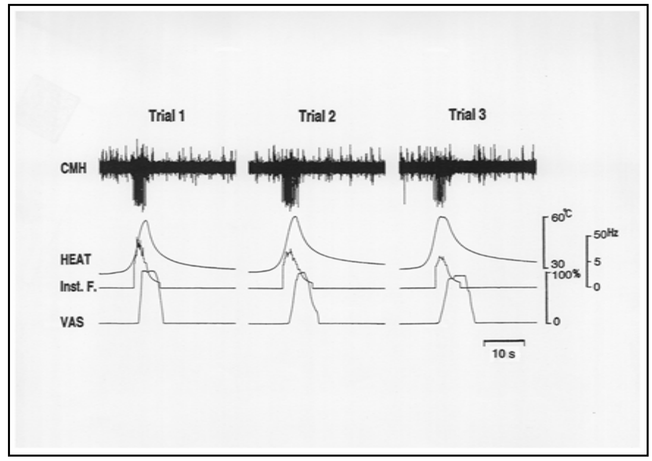

Figure 7

During the first application of moxibustion, the skin temperature reached an average peak of 62°C, whereupon the number of CMP firing impulses and instantaneous firing frequency also reached a considerably high frequency (average 37 imp and 49.4 Hz) and the subject felt a strong thermal pain. Yet, following the second application, even though the peak temperature reached during the moxibustion was approximately the same, a CHM firing desensitization is observed and the thermal pain sensation of subject is attenuated (Figure 8).

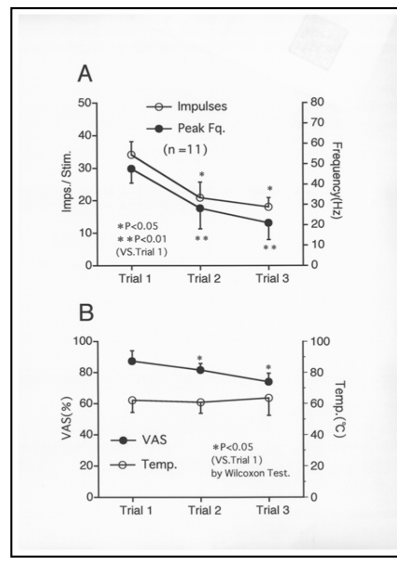

Figure 8

The attenuation of the thermal pain sensation thus observed after repeated application of moxa treatment is considered to represent a fatigue phenomenon[25]. Moreover, the high CMH firing frequency observed during the first moxa application may be expected to cause a central inhibition via the DNIC: diffuse noxious inhibitory control) [31].

2) A-fiber nociceptors

Human cutaneous nociceptors also include apart from the C-fiber polymodal nociceptor Aδ afferent nerve fibers[8,9,12,32].

Among the records obtained so far from human cutaneous afferent nerve fibers the number of units with a conduction velocity in the Aδ range are extremely few. This is also due to the fact that their proportion among the fibers within nerve trunks is compared to the CMH units low[33]. Among these, again, units are classified as units responding to both mechanical and thermal stimulation (A-fiber mechano-heat nociceptor: AMH) and receptors with a high threshold responding to mechanical stimulation only (high threshold mechanoreceptor: HTM) (Table 1) [34,35].

	CMH	HTM	AMH
C.V.(m/s)	0.96±0.17(n=239)	19.2±8.4(n=11)	23.5±10.2(n=15)
Mechanical Threshold (mN)	24.1±21.9(n=180)	29.1±12.6(n=239)	23.0±14.9(n=15)
Thermal Threshold (°C)	41.8±2.7(n=130)		49.1±1.4(n=12)

CMH: C Mechano Heat Nociceptor (mean ±S.D.)
HTM: High Threshold Mechano Nociceptor
AMH: A Mechano Heat Nociceptor

Table 1

The receptive fields of these units show a distribution of either single or multiple points sensitively responding to mechanical stimulation within cutaneous areas of fixed size, where the areas between the individual points have a high threshold for mechanical stimulation, or are not responsive at all. The terminals of these receptors have several branches within specified areas and form points responding sensitively to mechanical stimulation which are considered to be distinctly separate from the surrounding areas.

Morphological studies of high threshold mechanical receptors in hairy skin of cats clearly showed, that axons surrounded by Schwann cells are distributed among the terminals and the nerve endings are surrounded by keratinocytes. This increases the threshold toward stimulation and is considered to define the localization.

The characteristics of HTM and AMH receptors in response to mechanical stimulation show in any case, slowly-adapting firing patterns, transmitting intensity or variation components of nociceptive stimulation to the skin centrally. Both show about the same threshold for mechanical stimulation, which are at the same time of a similar magnitude of the threshold for mechanical stimulation of CMH. Originally nociceptors of A-fibers are thought to transmit the primary pain caused by nociceptive mechanical stimulation[36]. The localization of piercing the skin by tapping acupuncture needles is very distinct, so in that case it provokes stabbing pain, a high frequency firing activity of the AMH is induced[9].

On the other hand, burning the skin surface with moxa through direct moxibustion is a stimulation method definitely causing burns of the skin, in which case, the response of the AMH to the thermal stimulus is very important. Namely, the response of the AMH to the thermal stimulus is distinctly different from the response of the CMH. One of these properties has been demonstrated in units classified as type 1 AMH in hairy skin of monkeys and other animals[33,37,38], that are characterized by an extremely high threshold temperature for nociceptive thermal stimuli (Table 1).

In human AMH, the units that respond to thermal stimulation from the very beginning react at temperatures of 48 - 52°C. The firing starts after temperatures have reached this range and the subjects experience a strong thermal pain sensation (Figure 9).

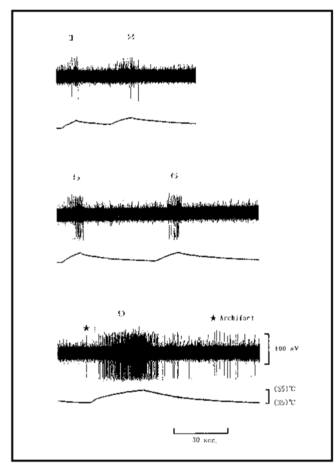

Figure 9

Again, depending on the unit, there are also some that do not show any firing during the initial phase of trials with repeated thermal stimulation, but after several preceding thermal stimuli of 50°C, causing the development of a mild degree of rubescence on the skin surface, the receptive field becomes sensitized to the thermal stimulation, after which the onset of firing is observed. Moreover, through repeated thermal stimulation, the relevant excitability is temporarily obtained so that the units show an obvious increase in firing in response to the thermal stimulation. In some units, high frequencies of up to 50 times per second may be observed (Figure 10)[9,13,33,34].

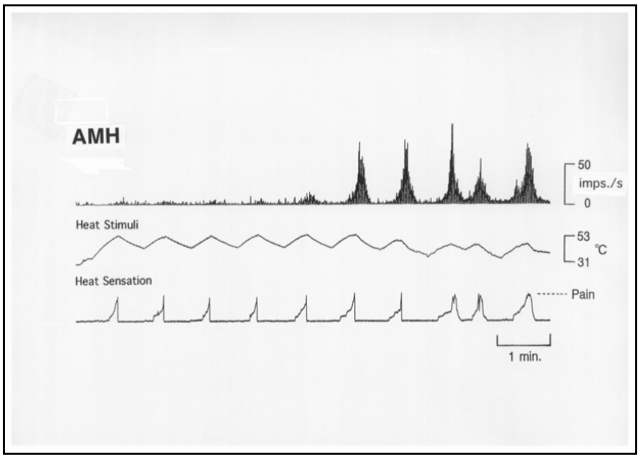

Figure 10

This degree of sensitization of the AMH in response to thermal stimulation which may be called dramatic does not occur in CMH. Here, both firing frequency and the degree of sensitization can be said to be distinctly different from that of the CMH[10]. Examination of the correlation between the firing activity of the AMH in response to thermal stimulation and the subjective sensation of heat pain in the subjects showed only a moderate degree of firing activity during the initial phase of a stimulation trial at a time when the excitability just started to develop, but this did not clearly correspond to a cross-modality matching induced appearance of subjective thermal pain sensation. However, with an increasing number of repetitions of the stimulation the firing activity of the AMH units gradually increased, while both the subjective thermal pain sensation and fluctuations in the firing of the units showed parallel variations that allowed recognition of a clear correlation between firing frequency and changes in the expressions used to describe the thermal pain sensation (Figure 11).

In this way the AMH are sensitized and the thermal pain is localized, allowing accurate transmission of its intensity. Moreover, this also indicates a central input of the hypersensitivity information appearing after the development of burns in response to the thermal stimulation[13,36].

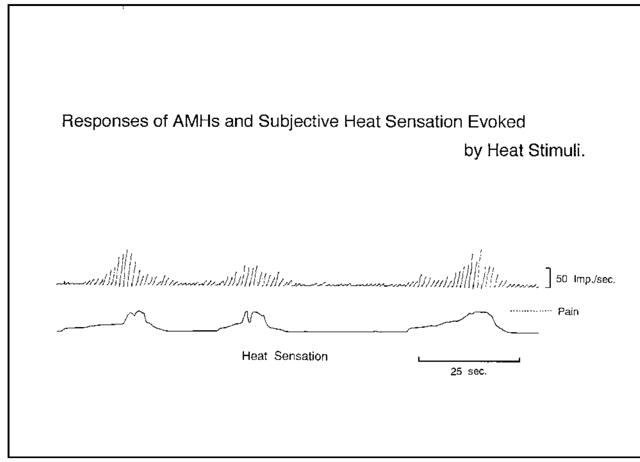

Figure 11

3) Nociceptors in deep tissues

Needling stimulation does not only excite nociceptors in the skin, but also nociceptors distributed in deep tissues like muscles or tendons and the like. In particular, the excitation of small diameter afferent fibers from deep tissue is more likely to elicit responses from the autonomic nervous or endocrine systems than it did in case of the skin, so that it has been pointed out, that the deep nociceptors are rather more likely to feed their information into the autonomic nervous or endocrine systems than the somatic nervous system[1]. Moreover, for the manifestation of acupuncture analgesic effects, excitation of the deep tissue nociceptors is considered to be important[2].

Units responding to needle stimulation of nociceptive fibers derived from human deep tissues (muscles) have the following characteristics[39].

All of the recorded units had conduction velocity in the Aδ range and spontaneous firing was not observed in any of these units. Further, areas from which firing could be evoked by electrical stimulation and their respective depths were markedly limited, and compared with the identification of cutaneous sensory receptive fields, their positions were not easy to determine. Also, they did respond only to mechanical stimulation within a restricted scope while in the presence of responses from proprioceptors, they did not respond to mild muscle contraction, stretching, or else vibrational stimulation. In response to pressure stimuli the firing increases depending in an intensity dependent manner. A good correlation is observed with the intensity of the sensation following pressure stimulation reported by the subjects. This can be considered to represent the transmission of sensory information pertaining to nociceptive mechanical stimulation.

Although this pertains only to a portion of the units, injection of the points most sensitive to mechanical stimulation with bradykinin (2 ml of a 1μg/ml solution) also induces firing and the pain induced by the bradykinin and reported by the subjects also increases in parallel with an increase in the firing frequency. The subsequent gradual decrease indicates a high probability that these are polymodal receptors (Figure 12A).

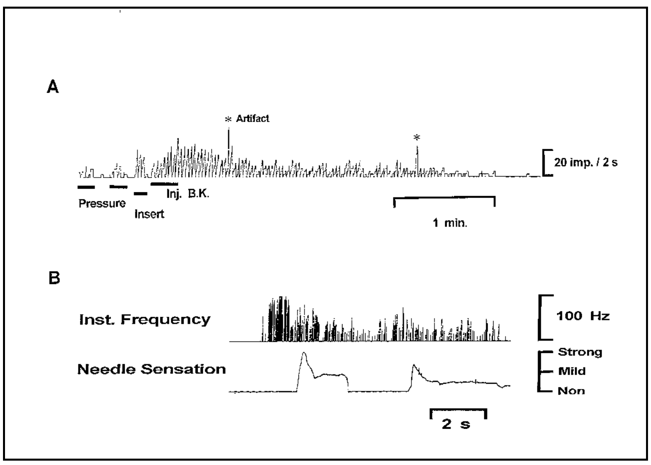

Figure 12

Upon performance of needling stimulation of the receptive fields of this type of muscular Aδ units, that is thrusting and lifting manipulation of muscles, these units definitely display a firing activity and in particular a synchronous high frequency firing was observed when the subjects experienced a de qi sensation. This observation shows the involvement of these units in the manifestation of de qi upon needling stimulation (Figure 12B).

Up to now the activity of C-fiber nociceptors has not been recorded from human deep tissue afferent nerves using microneurography nor found to be mentioned in the literature. In animal experiments, the activity of deep tissue C-fiber nociceptors in muscles and joints has been recorded and numerous relevant research reports[40,41] have been published. This suggests the possibility that regarding the recording of activities from human deep tissues there is some form of bias with the recording method using microneurography.

Since deep tissues are much less likely to be exposed to stimulation than the skin, the spatial distribution of the receptors themselves is conceivably narrower. Moreover, another possibility is the existence of silent nociceptors that under normal conditions are not sensitive to stimulation, that have been detected in muscles, joints, internal organs or the skin[42,43,44] .

These nociceptors are normally present in a concealed condition. In case of tissue lesions or inflammation acquiring excitability, after which they show excitability even for mechanical stimulation for which they had so far not been sensitive, are called chemo-specific nociceptors, or else noted as sleeping nociceptors. Through recruitment of the excitation of this type of nociceptors hyperalgesia or hypersensitivity can conceivably develop in the presence of inflammation[45,46,47] .

Accordingly, by creating minor tissue injuries through needling or moxibustion stimulation, the excitability of this new type of nociceptors is recruited and may be considered to carry hidden possibilities of having various effects on the body's defense system.

IV. Conclusions

The correlation between acupuncture and moxibustion stimulation has been described. Any of these stimuli probably uses cutaneous or deep tissue nociceptors as their main input system. Through excitation of these nociceptors, a negative feedback mechanisms exerts various effects on the body's defense system. Conceivably this can have a variety of effects, for example, the manifestations of an endogenous analgesic mechanism, triggering of responses from the autonomic or endocrine systems, or else modulation of the immune system. Moreover, these stimuli themselves produce some minor degree of tissue injury, leading to the release of algesic substances or modulators and their stimulation then cause retrograde stimulation of the receptors, subsequently probably exerting effects on the axon reflexes of terminals in the vicinity. Furthermore, through neurogenic inflammation the excitability of a new type of so far silent nociceptors is recruited, that then conceivably leads to both peripheral and central summation effects.

Through these mechanisms acupuncture and moxibustion are considered to cause via minor stimulation of the body surface, various clinical effects.

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Basic Research into Japanese Moxibustion – Introduction –

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Introduction

Therapy forms using heat stimulation of the skin are considered to have developed independently in numerous locations all over the world. Up to the present day a treatment modality closely resembling its original form is still used clinically in Japan and China. In particular, in Japan subtle changes have been made to adjust it to the characteristics of the people, numerous different forms of moxibustion have been contrived and are currently in use. Particularly noteworthy is form of moxibustion used currently in Japan. It is considered to have originated in Japan. It is seldom used in China, where the moxa is burned directly on the skin: direct moxibustion. This form of moxibustion differs from indirect moxibustion, where an attenuated heat stimulus is used like in stick moxibustion as a representative form of this treatment modality. It is considered not only to apply local warming, but rather also exerting considerable effects on distant sites like acupuncture. Yet, direct moxibustion causes, even if only temporarily, moxibustion marks. The heat stimulus when compared to indirect moxibustion is fairly strong and the preparation of the small moxa cones requires some skill so that recently its use has declined. It has not yet been properly investigated from the standpoint of which of these forms is the more effective one and whether there are possible differences in indications. Here I would like to present a brief summary of the research into moxibustion as it is performed in Japan, crude materials, the manufacturing process and the influence moxibustion has on the body.

Moxa raw material, manufacture, quality

The region of Ibukiyama has been famous as a growing district for moxa, but Oda conducted a detailed investigation of the subject and reported the following.[1] There are two sites called Ibukiyama: one in Shiga prefecture and another in Tochigi prefecture, both of which are famous production sites of moxa. The noted production site called Ibukiyama, that has been famous since the Heian period, is located in Tochigi prefecture, whereas Shiga emerged as a growing region following the Azuchi-Momoyama period. The Ibuki moxa varieties of both Tochigi and Shiga have their respective characteristics not found in the other location. Both Ibukiyama regions have a place called 'Shimeji ga Hara' and both regions have similar Buddhistic legends. By the Edo period, the Shiga region flourished, while the Tochigi region declined. Again, regarding the raw mugwort (yomogi) material botanical investigations were performed showing that most of the yomogi material from the Niigata, Toyama and Ishikawa prefectures was Artemisia princes Pamp, while some of it was oo-yomogi (yama yomogi = Artemisia Montana Pamp., whereas all the materials from Shiga prefecture was reportedly of the yomogi variety.[2] Regarding the growing conditions for yomogi, Aizawa et al. compared yomogi grown in sunlight and in shade and reported that the yomogi grown in sunlight is the better suited variety.[3] Regarding the manufacturing equipment Oda has conducted a detailed investigation. The investigation included such aspects as structure, size, power and scale of manufacture for the various types of machinery used during the yomogi manufacture. In particular, the rough stones for stone mortars are obtained from quarries from the upstream region of Itoigawa city in Niigata prefecture of which hornblende andesite or enstatite hornblende andesite materials are reportedly the main products. Reportedly each manufactory uses these stones in particular forms.[4]

Classified by their use, there are about 10 different product types. The moxa used for indirect moxibustion or needle warming moxibustion contains besides the principal component of the T-shaped cilia a fair amount of fragments of leaves or stalks, while superior quality products for direct moxibustion does not contain any impurities. Aizawa used electron microscopy for his related examinations and published a detailed report. This showed that the previously known T-shaped cilia themselves also show differences among high and low grade products and are related to the feel of the material when forming the little moxa cones.[5] Moreover, according to previous hypotheses, the temperature characteristics and fragrance of high grade moxa was considered due to the fat and oil content in the cilia, but the above mentioned report by Aizawa and the below described report by Shimomura showed[6], that is a mistake in that high grade moxa almost does not contain any oils or fats. It seems highly likely, that the fragrance of the moxa is due to the essential oils contained in the stalk cells of the T-shaped trichome.

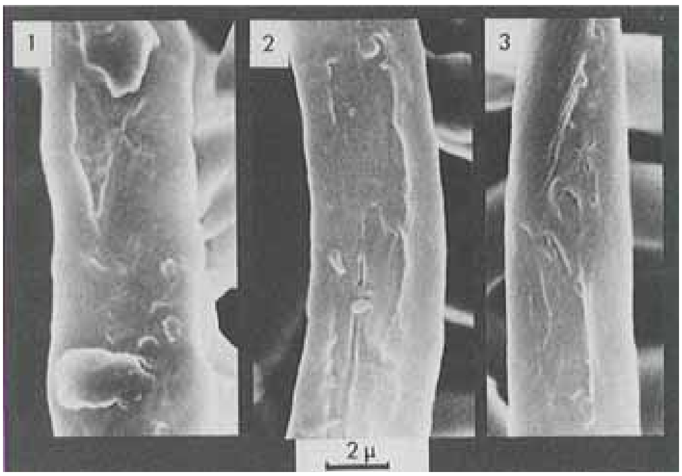


Photo: Comparison of T-shaped cilia of high and low grade products (1: low 2: medium 3: superior)

Essential oil components of moxa

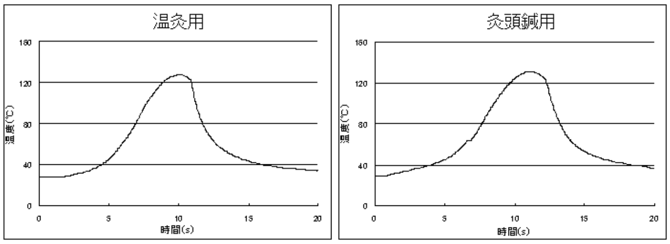
Nakao et a. reported that the moxa leaves contain approximately 0.02% essential oils of which the main component, comprising 50%, is cineol, followed by thujone, sesquiterpene alcohol and similar compounds, where the fragrance of moxa is most likely due to these components.[7] Yet, these reports deal mainly with the moxa leaves and are not the results of an analysis performed using therapeutic moxa material. Generally, moxa is said to contain tricosanol, hentricontane, arachinacohol, thujone and similar substances. In recent years, Toda et al. have identified n-non-acosane and n-hentriacontane using liquid gas chromatography[8] and the results of their essential oil component analysis of commercially available moxa (highest, high, normal grade) showed that the highest grade product contains lower saturated aliphatic hydrocarbons, but in high and normal grade products reportedly higher levels of saturated aliphatic hydrocarbons are present.[9]

Kobayashi et al. isolated from moxa a new tannin composed of the lipophilic heptatriacontene and catechols. Comparing the ratios by weight of the heptatriacontene and tannins among the various moxa varieties for a given moxa weight showed that the ratio by weight for heptatriacontene is approximately the same in all moxa varieties. However, the tannin content varies with the product quality, being low in the highest grade moxa and increased with increasing coarseness of the moxa. The combustion temperature – time curve for moxa treated to extract the lipophilic components und untreated moxa showed, that there were no differences in peak temperature, but for moxa from which the lipophilic components were extracted, the time required after ignition of the moxa to reach the peak temperature from 25°C increased and removing the heptatriacontene tended to make combustion more difficult. These workers thus reported that heptatriacontene affects the time for the rise in temperature in the combustion temperature – time curve.[10]

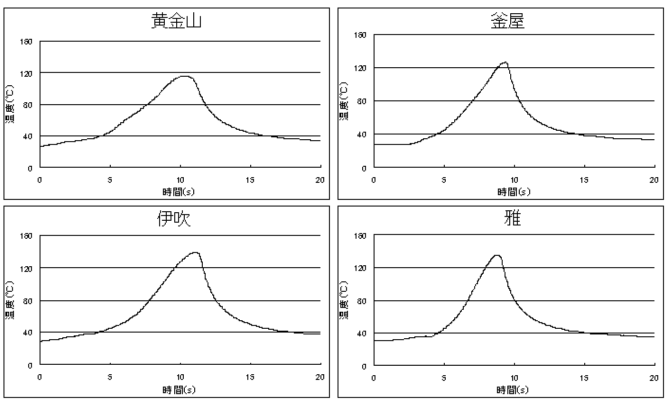
Temperature characteristics during moxibustion treatment

Reports pertaining to the temperature characteristics observed during direct moxibustion have been published for a long time[11], but few papers dealt with the amount of heat generated by the moxa and the large size of the temperature measurement probe did not allow exact measurements. Aizawa et al.[12] and Sugeta et al.[13] reported on their use of microscopic thermocouples to measure the temperature characteristics on and below the skin of mice. They reported that in contrast to what was believed in the past, skin temperature was significantly higher than 60℃, while the subcutaneous temperature was lower than the temperature on the skin and even continuous performance of moxibustion did not produce an increase in temperature proportional to the number of moxa cones burned. Commonly the fact that moxibustion treatment using low grade moxa felt hot was ascribed to a large amount of heat generated. Yet, quite recently, Aizawa's research showed that the difference in the amount of heat generated by different qualities of moxa is minimal and the effect is more likely due to differences in heat sensation and the burning technique.[14]

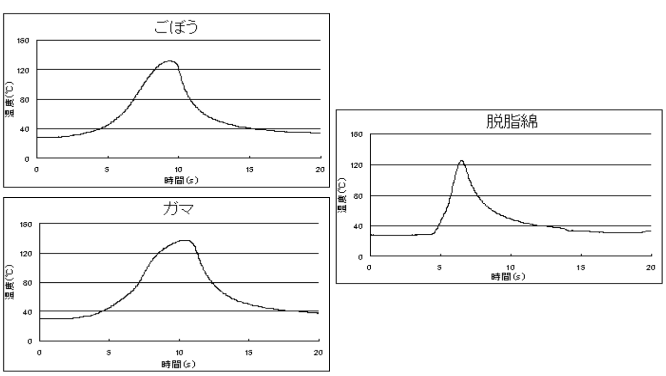
Figures: Moxibustion temperature curve



The left graph is for warming moxibustion
The right graph is for needle warming moxibustion
(vertical axis indicates Temperature (°C), and horizontal axis indicates Time (s).)



The upper left is Ogonzan; the upper right is Kamaya; the lower left is Ibuki; and the lower right is Miyabi.
(vertical axis indicates Temperature (°C), and horizontal axis indicates Time (s).)



The upper left is Burdock root; the right is Bulrush; and the lower left is Absorbent cotton.
(vertical axis indicates Temperature (°C), and horizontal axis indicates Time (s).)

Considerable research has been conducted into warming moxibustion or indirect moxibustion. Ozaki[15] and Ueda[16] performed a detailed examination of the temperature characteristics of moxibustion using a moxa tube or moxibustion on pedestals of intervening materials and reported considerable differences depending on products used regarding the temperature and its sustenance. Onishi reported that with indirect moxibustion, also used as frequently as warming moxibustion, it is not only the warming effect, but the components of the material used as pedestal may possibly also exert some effect.[17]

Tissue changes at the site of moxibustion treatment

Aizawa et al. observed the effects of direct moxibustion on mouse skin over a period of 14 days following treatment and found that after application of three moxa cones the skin had recovered almost to its normal state after 14 days, without moxa scar. In the case of treatment using 20 cones there was some hypertrophy of the epidermis after 14 days, but after about 20 days the skin was considered to have recovered almost to its normal state.[18] Menjo et al. electron microscopically observed morphological changes in cutaneous collagen microfibrils using both electron and light microscopy. He found that the local alterations were the most marked, where the greater the amount of moxa was and these effects did not disappear even after 24 hours. This is a highly interesting fact when considering the influence of the temperature reached during moxibustion treatment on the body. Moreover, the heat stimulus provided by moxa treatment on the one hand and burns on the other hand may be considered to differ in the degree of their invasiveness for the body and will need further study in the future. The effects of moxa treatment are considered to be mediated via local inflammatory reactions, but it should be taken into account that the term inflammation could imply that the effects of inexplicable heat stimulation may also be considered as being included in the moxibustion effects.[19] In this respect, this report was very interesting. In other words, burns in general and burns caused by moxibustion are completely different regarding the degree of invasiveness and size. Accordingly, the inflammatory reaction alone caused by a simple burn cannot conceivably be considered to have the effects moxibustion does. Rather, the heat stimulus applied during the moxibustion is considered to be important.

Influence of moxibustion on blood circulation

There are also many reports dealing with local and distant changes in blood flow. Takeda et al. have investigated the changes in local and distant cutaneous blood flow depending on the number of applied moxa cones and found that the application of a single moxa cone may produce locally a maximal increase of 580%, while application of 10 cones resulted in an increase of 720%. The stimulus intensity dependent increase in blood flow and sequential changes subsequently gradually decreased and returned reportedly after about 30 minutes to the control value set for the experimental time.

Almost no changes are observed in the peripheral blood flow after application of 1 cone, but moxibustion using 3 to 10 cones produced a transient reduction in blood flow that subsequently returned close to the control value, after which a tendency towards a slight increase was reportedly observed.[20] Ueda et al. applied various types of warming moxibustion to the forearm to examine the temperature characteristics and then used the laser Doppler method and a thermocouple thermometer to observe the changes in dermal blood flow both locally and on the dorsum of the hand as a distant reference site. In case of moxibustion on pedestals, the duration of the high temperature phase was short and the temperature curve cone-shaped, where the peak temperature varied with product type. For moxibustion using moxa tubes, the duration temperature was long and was maintained near the peak temperature with the temperature curve trapezoidal. Locally at the site of moxibustion an increase in blood flow was observed with all forms warming moxibustion, but the rate of increase depended on the peak temperature and quantity of the stimulus. Moreover, it was reported, that no obvious changes were observed in the periphery both in dermal blood flow and temperature. Yet, the rate of increase in blood flow increased with the quantity of the stimulus, but very strong warming moxibustion sometimes caused burns. There are marked individual differences in the rate of increase in blood flow and intensity of thermal pain sensation. Thus, these authors stated that it is important during clinical application of warming moxibustion to choose a type of warming moxa which provides a suitable quantity of stimulus within a scope not causing burns.[16]

Regarding indirect moxibustion, Matsuhata et al. performed "ginger moxibustion" on Ashi no sanri (zusanli, ST36) and observed the effects on the blood flow through the lower extremity and deep plantar tissue temperature. Local blood flow through the lower extremity increased over a period of 2 to 4 minutes following the stimulation, but no changes were observed on the contralateral side.[21] They also reported to have observed no changes in deep tissue temperature at the site of measurement. Recently, warming moxibustion providing a mild heat sensation tends to be favored, but there are certain differences pertaining to the changes caused in blood flow by direct and indirect moxibustion. Regarding the other actions, similar differences may well be expected. The lighthearted concept of moxibustion being the use of moxa, or else whatever is warm may also be called moxibustion needs to be revised. It seems necessary to investigate the different actions of direct, warming and indirect moxibustion.

Immune system, blood etc.

Furuya et al. performed moxibustion on mice to observe changes in phagocytosis using the carbon clearance method and reported an increase.[22] Effects on blood coagulation capacity have been reported by Sakamoto et al., observing a slight increase in liver function and obvious effects on the clotting system.[23] Okazaki et al. examined the influence on blood clotting capacity and observed a tendency toward activation of the coagulation induced by burning a single cone of moxa, but intermittent continuous moxibustion apparently did not maintain this increase. Moreover, platelet aggregation tended to be inhibited over a period of 1.5 hours after application of 5 mg of moxa, while after application of 15 mg of moxa a tendency towards ATP release over a period of 1 hour, as well as a tendency towards shortening of the lag time by 1 to 5 hours was observed. ADP induced platelet aggregation after application of 15 mg of moxa showed a tendency towards continued elevation over a period of 24 hours, while the moxa application produced in both the 5 and 15 mg treatment groups an apparent increase in ATP after 1 and 3 hours respectively. The above results showed that a single application of moxa produced responses in the platelet system of mice that were not observed after intermittent continuous moxibustion stimulation, so that in case of a repeated moxa stimulation the effects may be considered to disappear.[24]

Matsukuma et al. applied an amount of moxa used during daily clinical practice in humans (0.3 mg of moxa, 5 cones) for the treatment of adjuvant arthritis in rats on a point corresponding to Ashi no sanri (zusanlin, ST36) in humans and reportedly observed an anti-inflammatory effect.[25]

While the amount of moxa usually used in clinical practice on humans when applied during research using normal animals is relatively greater, no obvious changes were obtained. In contrast, in research using animal disease models the amount of moxa usually used during daily clinical practice in humans produced observable effects. Thus, since the stimuli of acupuncture and moxibustion are very subtle, it may conceivably be difficult to demonstrate their effects during experiments using normal animals.

hsp

After maintaining the subcutaneous temperature for 15 minutes at 45℃ and within the muscle layer at 39-40℃ following the application of moxibustion, extraction of proteins from the gluteal regional muscle samples obtained after 3 and 24 hours showed that 3 hours after the performance of moxibustion on rats hsp70 and hsp71 were detected. Immediately after the moxibustion and 24 hours after it hsp71 was detected in the rats, hsp70 was not observed. Hsp71 was observed, however, in the control rats. Heat shock proteins (hsp) are synthesized as one form of physiological stress proteins. This suggests that the local application of heat in the form of moxa stimulation leads to the synthesis of hsp and thus exerts a physiological effect.[26][27]

These reports indicate that hsp are involved in the modes of action of moxibustion so that warming moxibustion provides a method of increasing hsp. Yet, while methods to increase hsp concentration generally require a certain degree of equipment and time, moxibustion can be considered to be a very simple method to achieve an increase in hsp concentration.

Anti-ageing

Sakamoto et al. investigated the effects of moxibustion treatment on age induced locomotor ataxia using Marshall's method applied to 4- and 9-month old Wistar female rats, treating the animals continuously at a rate of once per week with a total amount of moxa of 15 mg/body on points corresponding to Hyakue (Baihui, GV20) and Keimon (Jingmen, GB25). Regarding the vigor, no significant improvements in the locomotor ataxia were observed, the moxa treatment caused some improvements in locomotor ataxia regarding success.[28][29][30][31]

Since anti-ageing has recently become a common topic, this report suggests that moxibustion treatment may be expected to have some anti-ageing effects.

Antioxidation

For a methanol extract of moxa and the combustion products of moxa, radical, eliminating effects have been observed.[32]

Activity differs depending on the type of moxa, where the radical eliminating activity of warming moxa was weak, but that of moxa for direct moxibustion strong. Based on these results, it was considered that the inhibiting activity of moxa for direct moxibustion of lipoperoxidation is stronger than that of warming moxa.[33]

The above described results show that there are differences between direct moxibustion and warming moxibustion. As described above, the differences in the effects of direct, warming and indirect moxibustion are considered to require further thorough investigation.

Closing remarks

It is not easy to introduce all the research pertaining to the entire scope of moxibustion induced actions. Research into the both ancient and modern treatment modality of moxibustion is progressing with results used in treatment form for people of the world.

It is my goal to finish my research results in the hope that this treatment form may be helpful for promoting health.

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