– Correlation between Nocicepetion and Acupuncture and Moxibustion –

Yukihito Sugawara
Department of Basic Medical Research
Tokyo Eisei Gakuen College

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.

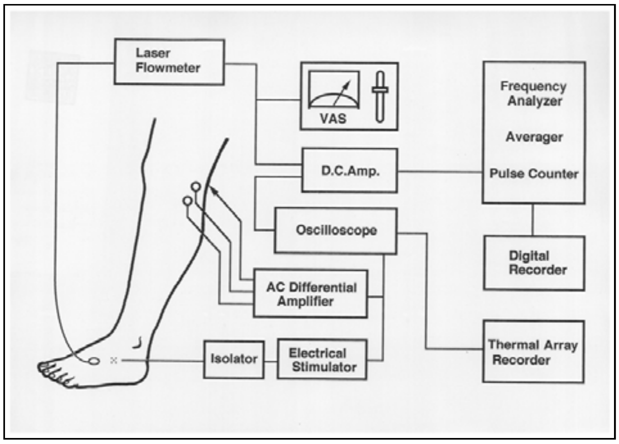

Figure 1

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.

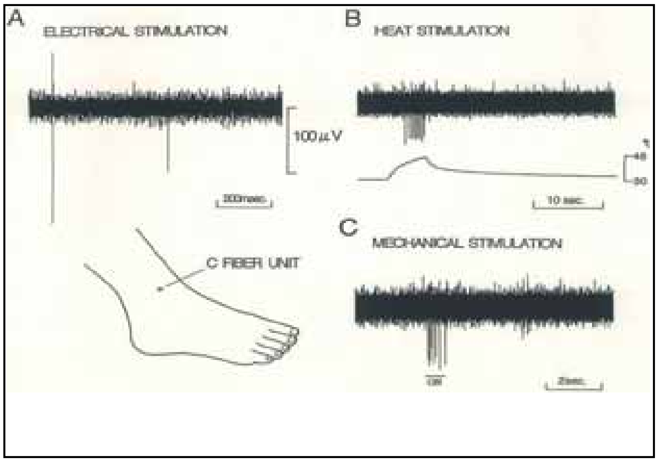

Figure 2

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.

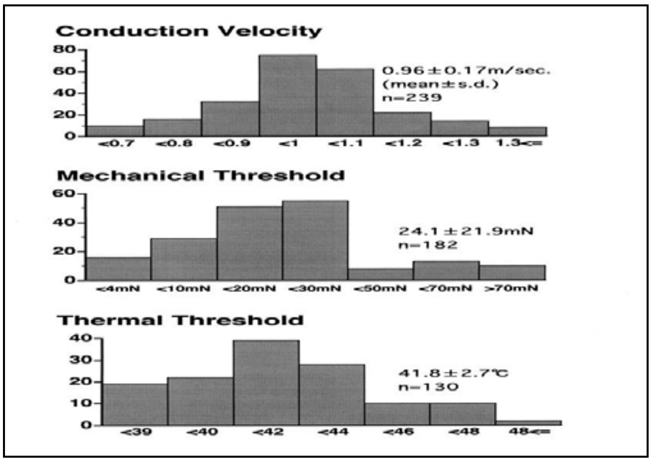

Figure 3

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).

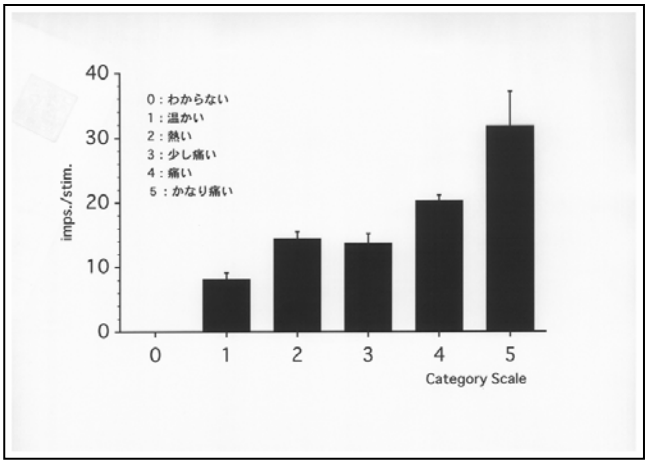

Figure 4

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.

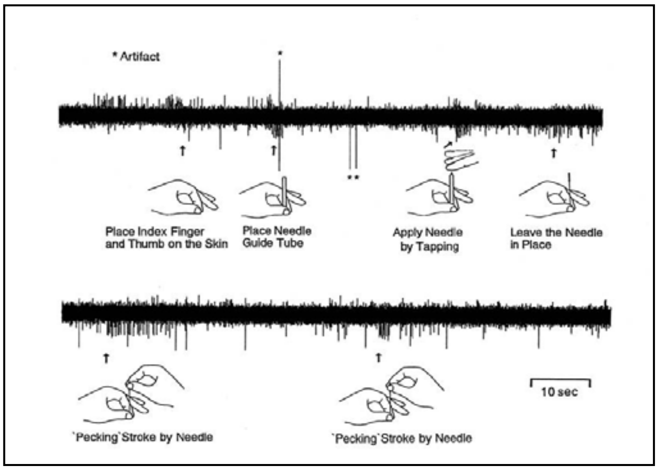

Figure 5

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.

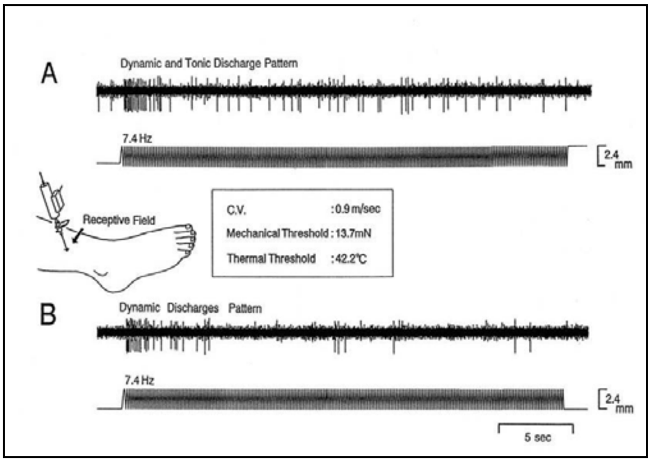

Figure 6

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.

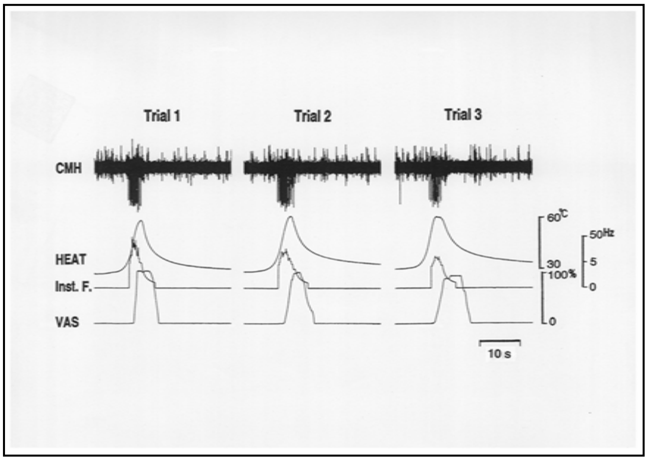

Figure 7

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).

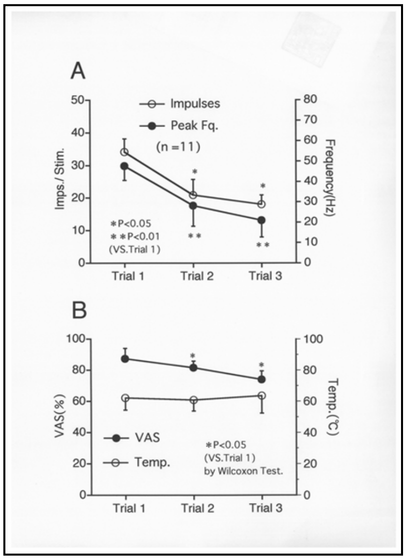

Figure 8

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).

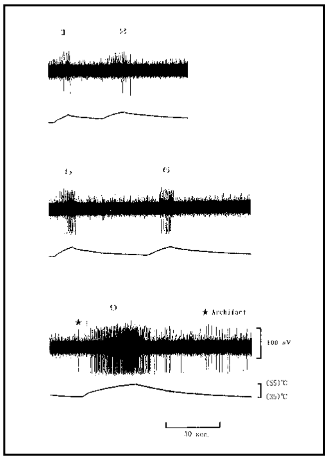

Figure 9

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).

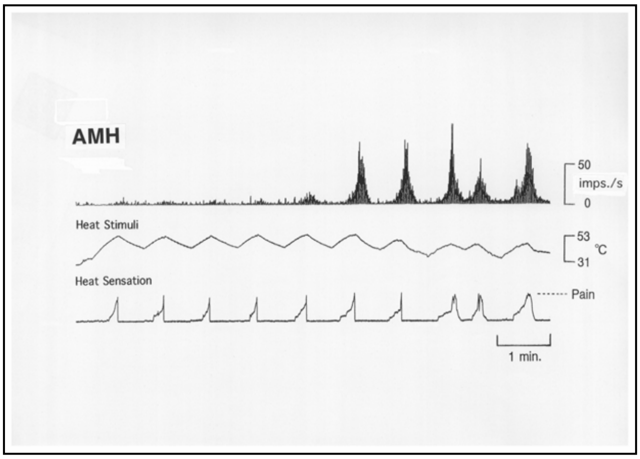

Figure 10

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 CMH10). 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 stimulation13,36).

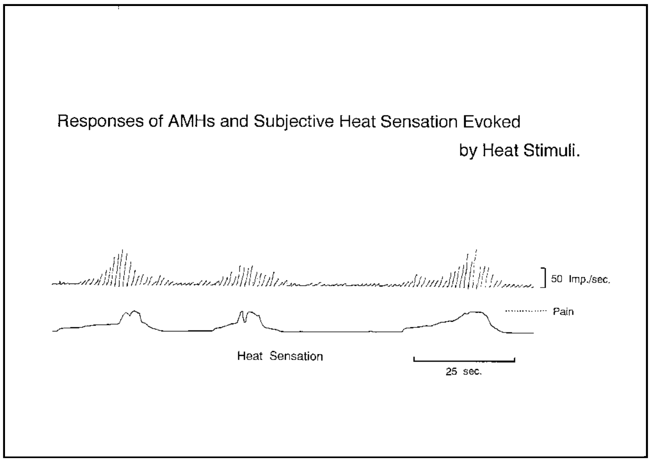

Figure 11

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 system1). Moreover, for the manifestation of acupuncture analgesic effects, excitation of the deep tissue nociceptors is considered to be important2).

Units responding to needle stimulation of nociceptive fibers derived from human deep tissues (muscles) have the following characteristics39).

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).

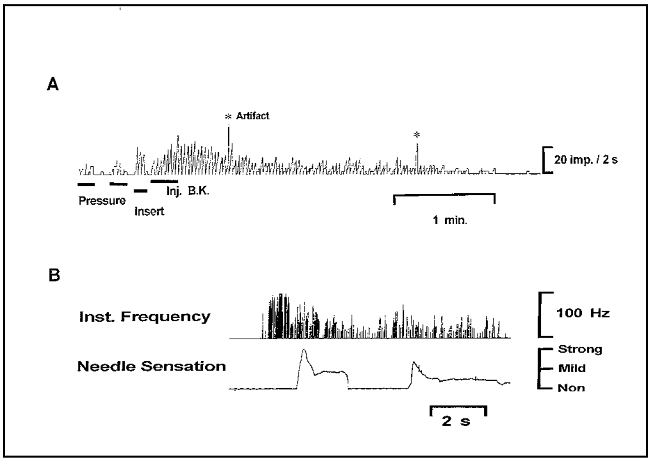

Figure 12

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 reports40,41) 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 skin42,43,44) .

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 inflammation45,46,47) .

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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