

# Mechanisms of action of acupuncture for chronic pain relief – polymodal receptors are the key candidates

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## **Abstract**

Therapeutic benefits of acupuncture for chronic pain patients have been clearly identified in recent clinical trials. Underlying mechanisms of acupuncture action mediated by endogenous opioids have been well demonstrated. The existence of pain inhibitory systems in the central nervous system has also been clarified and acupuncture seems to be a potent stimulus for activating the analgesic systems, although the pain mechanisms in acute and chronic states are essentially different. On the other hand, the exact nature of the acupuncture point still remains unclear. Here, we propose a key role of polymodal receptors (PMR) in acupuncture and moxibustion and offer a rational explanation of the acupuncture point as a sensitised PMR.

Moxibustion (burning of moxa) therapy has been shown by medical historians to predate the use of acupuncture, and the meridian theory developed in association with moxibustion treatment. A variety of sensory receptors are activated by acupuncture and/or moxibustion, but there are very few that can be excited by both stimuli. PMRs are one of the most promising candidates. The functional characteristics of PMRs correspond with those of acupuncture action in the periphery; and tender or trigger points, one of the primitive features of acupuncture points, are assumed to be the sites of sensitised PMRs. Diffuse noxious inhibitory control (DNIC) is proposed as a possible mechanism of immediate action of acupuncture, and inputs for the development of DNIC seem to be the PMRs.

In our experimental model, repeated eccentric contractions of muscle produced local tenderness at the palpable band and induced a typical referred pain pattern on application of pressure. Repeated indomethacin injections inhibited the production of the experimental trigger point.

These lines of evidence suggest that the acupuncture points are the sites where the PMRs are sensitised and that such conditions might be repeatedly produced by various biomechanical stressors, insufficient blood supply and metabolic products.

## **Keywords**

*Acupuncture, moxibustion, polymodal receptor, acupuncture points, trigger points, diffuse noxious inhibitory controls (DNIC).*

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## **Introduction**

Recent clinical trials have clearly demonstrated that acupuncture can induce significant pain relief in various chronic pain patients such as myofascial pain syndromes,<sup>1</sup> fibromyalgia,<sup>2,3</sup> and osteoarthritis of the knee.<sup>4,5,6</sup>

The mechanism of chronic pain has been shown to be essentially different from that of acute pain.<sup>7</sup> Plastic changes of synaptic connections in the central nervous system are of major importance in various types of chronic pain. In these cases, conventional drug therapy

with simple analgesics is usually not effective,<sup>8,9</sup> as the target is not the pain transmission systems from the injured tissues. It is therefore important to know how acupuncture and moxibustion may act on such chronic pain patients to induce analgesic effects.

It has been well established that acupuncture induces slowly developing general analgesic effects, and these are mediated by various endogenous opioids. These findings have been well recognised as the scientific bases of the mechanism of acupuncture until now.<sup>10</sup>

On the other hand, the general procedure for acupuncture for chronic pain patients is to insert needles into certain acupuncture points, manipulate them, and retain them for several minutes. After treatment, patients report immediate pain relief in some cases. These clinical procedures may be different physiologically from electroacupuncture (EA), which is used in the experiments in conscious animals, and may indicate the existence of different mechanisms of action for these different modalities of acupuncture.

In this brief review, various analgesic mechanisms that participate in the actions of acupuncture and moxibustion are summarised, and a possible explanation is proposed for acupuncture points through the functional and morphological characteristics of polymodal receptors.

#### *Mechanisms of electroacupuncture analgesia (EAA)*

The neuropharmacological basis of electroacupuncture analgesia (EAA) has been well established by a series of animal experiments. EA produces a gradual development of general analgesic effects of sustained duration. Naloxone, a recognised opiate receptor antagonist, clearly inhibits the development of EAA.<sup>11</sup> A series of animal experiments using various receptor antagonists and antisera of opioid peptides demonstrated the participation of different endogenous opioids and their receptors in EAA induced by different frequencies of EA.  $\beta$ -endorphin, enkephalin and dynorphin were released selectively by 2, 15/30 and 100 Hz respectively. Cholecystin cytokinase (CCK) was also identified as an endogenous antagonist of acupuncture analgesia (AA).<sup>12,13</sup>

The existence of endogenous pain inhibitory systems in the central nervous system (CNS) has also been well documented. Electrical stimulation applied to certain brain sites, called stimulation produced analgesia (SPA), induces potent analgesia; focal injection of morphine can induce analgesia dependent on the injection site; and immunohistochemical staining studies clearly demonstrate the different distribution patterns of opioid receptors in the CNS. These data strongly suggest the existence of common pain inhibitory systems including the arcuate nucleus in the hypothalamus, periaqueductal grey (PAG), parabrachial nucleus (PBN), rostral

ventromedial medulla (RVM), and descending inhibitory systems originating from the nucleus raphe magnus (NRM) and locus coeruleus (LC) as key substrates in the CNS.<sup>10,14</sup>

Based on these lines of evidence, Han proposed the endogenous opioid theory of EAA,<sup>10</sup> which has been widely accepted as the mechanism of action of acupuncture until now.

It should be noted, however, that these experiments were conducted in an acute pain model using normal conscious animals, so they may not fully explain the actions of acupuncture in chronic pain. In a pathological pain condition, peripheral opioid receptors play a significant role in the analgesic action of EA.<sup>15</sup> Moreover, analgesia induced by EA with the intense current used by Han's group seems to be different from that obtained in chronic pain patients. For example, brief, gentle acupuncture manipulation for deactivating active trigger points is strongly recommended in the treatment of patients with chronic muscle pain.<sup>16</sup> These procedures in clinical acupuncture are quite different from the form of EA widely used in basic research on EAA.

#### *Afferent inputs for activation of the pain inhibitory systems*

It is common knowledge that stimulation with electric current activates various types of receptors and nerve fibres. A recent neurophysiological study demonstrated that almost all types of afferent receptors could be activated by manual acupuncture,<sup>17</sup> so it is important to clarify the responsible candidates for the analgesic action of acupuncture manipulation as well as EA.

Figure 1 summarises possible afferent inputs for the activation of endogenous pain inhibitory systems. Both thin ( $A\delta$  and C) and thick ( $A\beta$ ) afferents can activate the system through different mechanisms.

Analgesia induced by conditioning  $A\beta$  fibre stimulation in the form of EA with low intensity and high frequency current is assumed to be the same as with TENS.<sup>18</sup> These phenomena can be explained by the gate control theory.<sup>19</sup> In the early investigations of acupuncture analgesia, the important role of thick afferent fibres ( $A\beta$  fibres) was stressed.<sup>20</sup> However, the ancient medical literature found in the *Ma Wang Dui* tomb clearly demonstrated that the concept of meridians was born from clinical experience with moxibustion, not with acupuncture.<sup>21</sup> Therefore thick

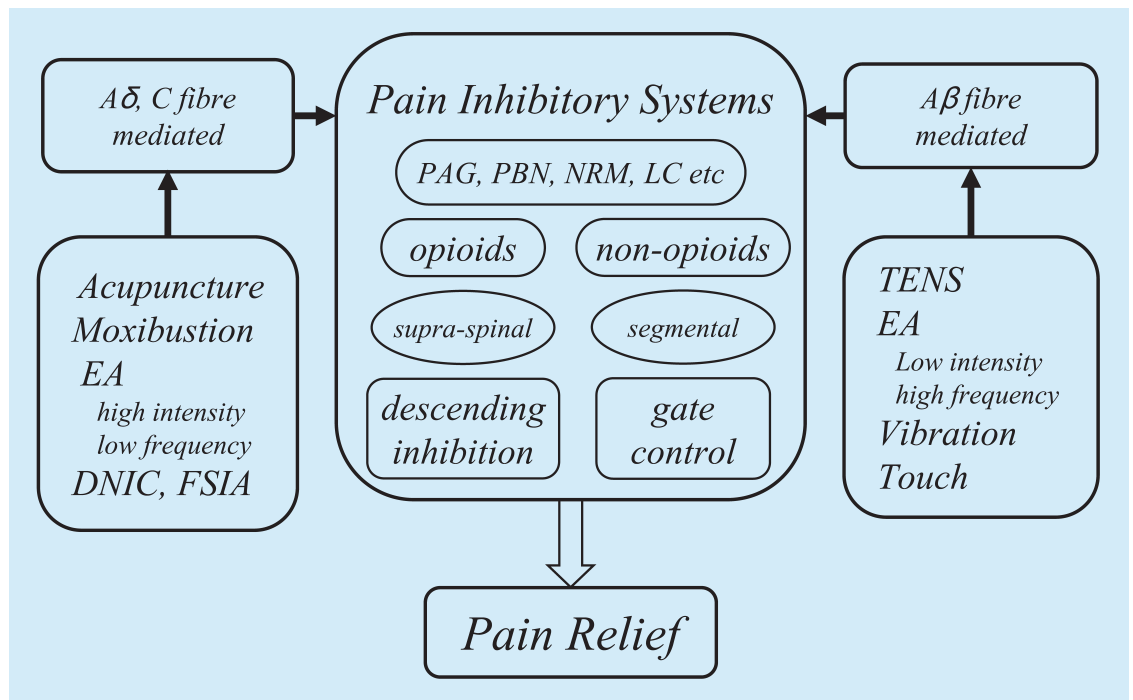


Figure 1 Schematic illustration of inputs for the activation of the pain inhibitory systems. Both thin ( $A\delta$  and  $C$  fibres) and thick ( $A\beta$  fibre) afferents activate the pain inhibitory systems. Moxibustion (heat) is the primitive input and polymodal receptors are the common candidate of acupuncture and moxibustion and DNIC (see text for detail).

(Figure cited with permission)

afferent fibre receptors should be excluded as candidates for the basis of acupuncture and moxibustion mechanisms because they are not responsive to heat stimuli such as moxibustion.

On the other hand, the role of thin afferent fibre inputs to the pain inhibitory systems is also well established. EA of high intensity and low frequency has been assumed to be the typical parameter for EAA mediated by endogenous opioids. Selective activation of the  $A\delta$  fibres in the peripheral nerve by triangular shaped stimulus pulses as well as EA at 5Hz produced a significant suppression of the jaw opening reflex (JOR).<sup>22</sup> Electric shock applied to the paw also induced endogenous opioid mediated analgesia dependent on the site of stimulation and parameters of electrical shock used, and the author assumed the EAA to be part of foot-shock induced analgesia (FSIA).<sup>23</sup>

An interesting phenomenon of pain inhibition was first reported by Le Bars and named as diffuse noxious inhibitory controls (DNIC).<sup>24</sup> Neural activity of the nociceptive neurons in the medullary dorsal horn are rapidly suppressed by the conditioning

stimulation applied anywhere on the whole body (face, limbs and tail), and in every tissue stimulated (skin, muscle, viscera).

Figure 2 demonstrates the results of two experiments showing DNIC-like analgesic action induced by acupuncture and thermal and/or chemical stimulation.<sup>25,26</sup> Bing et al clearly demonstrated that immersion of the hindpaw in hot water clearly suppressed the nociceptive neural discharges evoked by electrical stimulation applied to the receptive fields (2A-left).<sup>25</sup> In addition, manual acupuncture to the *Zusanli* point (ST36) induced similar suppression of the pain response of the same neuron (2A-right). Both effects were partially antagonised by naloxone administration in a time-dependent manner.<sup>25</sup> Figure 2B shows that intramuscular injection of bradykinin (BK) and thermal stimulation to the fascia of the muscle have suppressive effects on the jaw opening reflex (JOR) elicited by tooth pulp stimulation. The time-courses and degrees of naloxone reversibility were quite similar.<sup>26</sup>

Regarding the afferent inputs for the DNIC-like phenomena, receptors responsive to noxious thermal

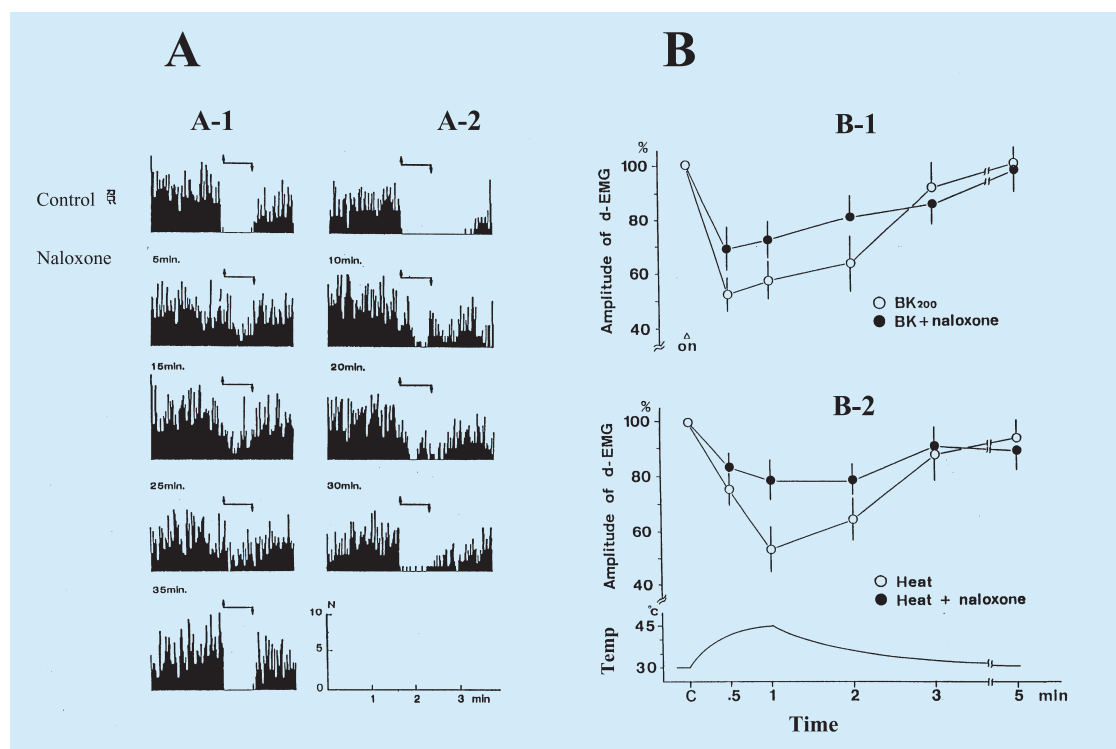


Figure 2 Similarity of DNIC and acupuncture analgesia:

A-1 Immersion of rat hind-paw into hot water clearly suppresses the nociceptive neural discharges evoked by the electrical stimulation applied to the receptive fields

A-2 Manual acupuncture to Zusanli (ST36) induces similar suppression of the pain response of the same neuron. Both suppressions are partially antagonised by naloxone time-dependently

B-1 Jaw opening reflex (JOR) is suppressed by intra-muscular injection of bradykinin (BK)

B-2 JOR is suppressed by thermal stimulation applied to the fascia.

Similar rapid suppressions of JOR were induced by both BK and heat stimulation. Pre-administration of naloxone (1.0 mg/kg, ip) partially antagonised the suppressive effects of both chemical and thermal stimuli. (Modified from ref 25, 26; Figure produced with permission)

(hot water immersion), mechanical (pinching), and chemical (bradykinin) stimulations were required, and polymodal receptors are suggested as a possible candidate.<sup>26</sup>

#### Characteristics of polymodal receptors and their role in acupuncture and moxibustion

Polymodal receptors (PMRs) have been proposed as a common candidate for the modes of action of acupuncture and moxibustion stimulation as they can be activated by both thermal (moxibustion) and mechanical (acupuncture) stimulation.<sup>27</sup>

Polymodal receptors are not typical nociceptors as they have a relatively low threshold and wide dynamic range responses, and they are easily sensitised (showing decreased threshold and increased magnitude of response) by various

chemical substances such as prostaglandins (PGs), histamine and bradykinin (BK), etc. They also have effector function, that is, they can release various neuropeptides eg substance P (SP) and calcitonin gene related peptide (CGRP) from their receptor terminal, and these neuropeptides induce inflammatory responses through receptors on blood vessels. It is well known that acupuncture and moxibustion provoke a flare and wheal response around the site of stimulation.<sup>26</sup> The flare (vasodilatation) and wheal (extravasation) have been shown to be the result of antidromic activation of polymodal-type thin afferent fibres,<sup>28</sup> and it has been clearly demonstrated that antidromic electrical activation of an identified single PMR afferent fibre produces a spot-like blue dye extravasation in its receptive field.<sup>29</sup>

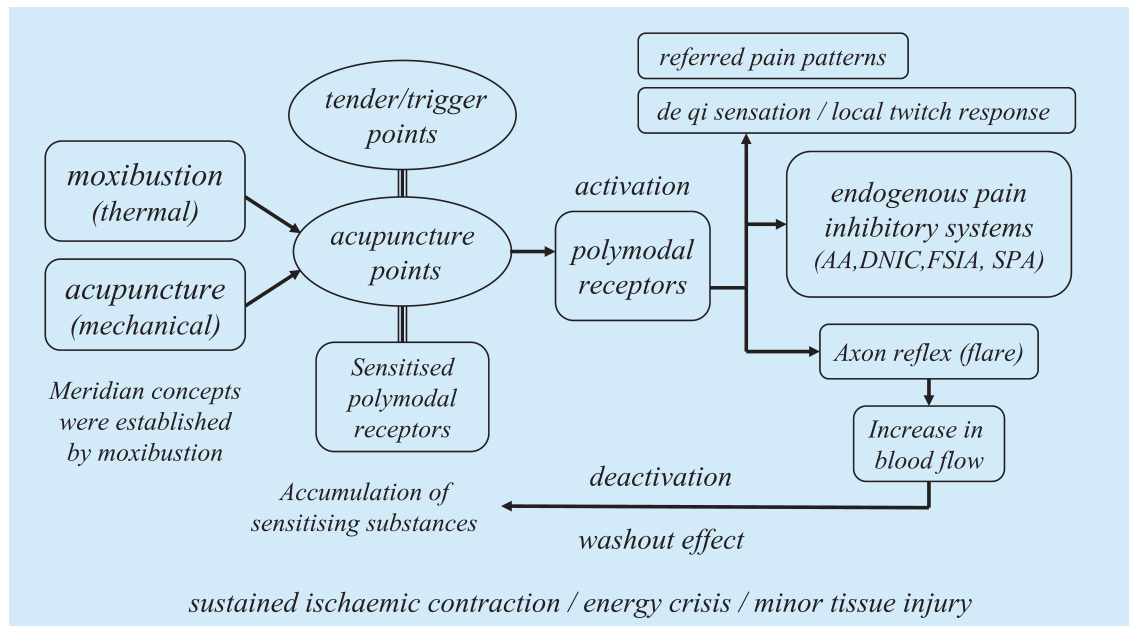


Figure 3 Schematic illustration of the participation of polymodal receptors in acupuncture and moxibustion action to the acupuncture/trigger points.

Polymodal receptors can be activated by both acupuncture and moxibustion. A major feature of acupuncture points is their tenderness. Sensitisation of the PMRs is a possible explanation for this tenderness. Thus, the existence of sensitised PMRs in acupuncture points and trigger points may provide a major functional basis for understanding the clinical significance of these points in both acupuncture and moxibustion treatments. The morphological characteristics of acupuncture points are also similar to those of PMRs (Table 1).

#### *Close relationship between acupuncture points and trigger points*

Wide distribution through various tissues throughout the body and lack of specific structures are morphological characteristics of the acupuncture points,<sup>30</sup> although a recent study suggested the existence of a threadlike structure resembling the Bong-hang duct.<sup>31</sup> Tenderness has been one of the clearest physiological characteristics of acupuncture points since ancient medical literature. Our previous survey also clearly demonstrated that tender points and palpable bands, as well as formal acupuncture points, were used in clinical treatment by well trained Japanese acupuncturists.<sup>32</sup>

On the other hand, trigger points are found in chronic muscle pain patients with myofascial pain

syndrome (MPS). Trigger points are characterised by their tenderness to pressure at the precise point on the palpable band, and the induction of specific referred pain phenomena recognised by the patient.<sup>33</sup>

Melzack reported that the location of trigger points in patients with MPS was in close agreement with the location of acupuncture points.<sup>34</sup> The concept of the trigger point is established from the modern Western medical treatment of pain without any knowledge of the traditional Chinese medicine. On the other hand, the distribution of tender points in patients with fibromyalgia was also shown to be quite similar to that of acupuncture points.<sup>35</sup> These similarities of location of trigger and/or tender points to those of acupuncture points suggest that a common pathophysiological mechanism might exist in the process of their development.

The concept of the meridian system has been considered an essential part of the theoretical basis of acupuncture, even though it was established from clinical experience with moxibustion therapy. A sensory phenomenon called propagated sensation along the channel (PSC) has been considered as a clue to understanding the meridian system. These PSC phenomena seem to be sensory events in the central nervous system, and similar to the phenomena of the specific referred pain pattern elicited by trigger point stimulation.<sup>16</sup>

**Table 1 Functional and morphological characteristics of polymodal receptors and their relation to acupuncture and moxibustion stimulations and to acupuncture points and tender/trigger points**

	<b>Polymodal Receptors</b>	<b>Acupuncture and Moxibustion</b>	<b>Acupuncture Points</b>	<b>Tender/Trigger Points</b>
<b>Nature</b>	A kind of nociceptor (WDR)	Noxious stimuli, but not always painful, may be comfortable	<i>ah shi</i> point, point tender to pressure	Trigger the patient's chronic pain symptoms
<b>Function 1</b>	Responsive to mechanical, thermal and chemical stimuli	Acupuncture (mechanical) Moxibustion (thermal)	Sensitive to acupuncture and moxibustion	Sensitive to pressure and acupuncture needling
<b>Function 2</b>	Effector function – neurogenic inflammation is induced by antidromic excitation (flare, oedema)	Flare and oedema are produced by acupuncture and moxibustion	Sensitive to acupuncture and moxibustion	Local twitch response
<b>Function 3</b>	Considered to be inputs for bioregulatory systems	Effects on bioregulatory systems	Input to bioregulatory systems through meridians	Deactivation is important
<b>Pathogenesis</b>	Sensitisation by various chemicals – PGs, histamine, BK etc	Induce minor tissue injury; produce various inflammatory substances	Sensitised nociceptor	Sensitised nociceptor
<b>Structure</b>	Free nerve endings; co-existence of various receptors –TRP, B, EP, H, P2X, $\alpha$ , etc		No morphological characteristic is found	Sensitised nociceptor, local contracture and/or oedema
<b>Distribution 1</b>	Whole body, head, face, neck, arms, torso, legs and ears	Whole body surface is target for acupuncture and moxibustion	Distributed over the whole body	Often co-located with acupuncture points
<b>Distribution 2</b>	Skin, fascia, periosteum, ligament, muscle, vessels, viscera etc	Superficial (dermal) and deep (muscle, fascia etc) are used	Distributed through various tissues	Distributed through muscle and possibly other soft tissues

WDR = wide dynamic range; PGs = prostaglandins; BK = bradykinin; TRP = transient receptor potential family (TRPV1 = capsaicin, proton, heat receptor); B = bradykinin receptor. EP = prostaglandin E receptor; H = histamine receptor; P2X = ATP receptor;  $\alpha$  =adrenergic alpha receptor

Table 1 summarises the functional and morphological characteristics of the PMR and their close relationship to acupuncture and moxibustion stimulation, to acupuncture points, and to tender/trigger points.

#### *Pathogenesis of trigger point formation*

Regarding the formation of tender points, the sensitisation of the nociceptors such as the polymodal receptors is considered to be the most probable mechanism.<sup>26</sup> On the other hand, various working hypotheses have been proposed for the pathogenesis of the trigger points because of their complicated characteristics. One well known hypothesis was the contracture and energy crisis proposed by Travell and Simons.<sup>29</sup> Minor injury in the muscle tissues induces

the release of calcium ions from the endoplasmic reticulum of the muscle cell which triggers the contraction of muscle without electrical activation of the muscle membrane. The contracture of muscle suppresses the oxygen supply to the muscle and the consequent ischaemia releases various chemicals which sensitise the nociceptors.<sup>36</sup> However, electrical activity in active trigger points was reported in MPS patients.<sup>37</sup> After these new findings, an integrated hypothesis was proposed. The key concept is excess release of acetylcholine at the endplate which provokes endplate spikes and produce contraction knots and the energy crisis that sensitises nociceptors.<sup>38</sup>

In contrast, we have developed an experimental model of trigger points, tender points, palpable band,



referred pain pattern and EMG activity using repeated eccentric exercises,<sup>39</sup> and proposed the sensitisation of polymodal receptors as the key phenomenon. Injection of indomethacin completely abolished the development of such trigger point-like loci in rabbit.<sup>40</sup> One recent investigation using microdialysis technique strongly supported our hypothesis that various sensitising chemicals such as prostaglandin, histamine, bradykinin and inflammatory cytokines exist in high concentration at trigger points in humans.<sup>41</sup>

We should note that tender points can develop not only in the myofascial tissues but also in ligaments, periosteum and other sites. The integrated hypothesis of trigger point formation cannot offer a rational explanation of the developments of these non-myofascial tender points which are frequently detected in patients with muscle pain syndromes.

### *The referred pain phenomena and chronic muscle pain*

The most impressive phenomenon for patients with MPS is that the true source of their symptom such as headache does not exist in the head. Trigger points located in a remote region cause referred pain projecting to the head, that is, the subjective symptomatic pain they felt is the referred pain phenomenon which developed within the CNS.

Intramuscular injection of hypertonic saline induced specific patterns of referred pain depending on the site of injection.<sup>42</sup> The physiological mechanism of referred pain has been well documented in animal experiments. The convergence-projection theory was the most popular and was supported by numerous experiments. However, the experimental referred pain phenomena arising in human subjects involves a delay of at least 10 seconds, and the simple convergence-projection theory cannot explain this delay.<sup>43</sup> On the other hand, the neural plasticity of spinal convergent neurons in referred pain-like phenomena was nicely demonstrated in myositis rats.<sup>44</sup> Intramuscular injection of bradykinin induced the appearance of a new receptive field or an expansion of the receptive fields in convergent neurons, and the changes in the receptive field might be the results of plastic changes of synaptic transmission mediated by various neurotransmitters (convergence-facilitation). N-methyl d-aspartate (NMDA) receptors were supposed to be a possible candidate for such plastic synaptic

changes related to the referred phenomena of muscle pain. Recent progress in research on NMDA receptor antagonists for treatment of chronic pain indicates that a proportion of chronic pain patients might be treated by acupuncture and moxibustion through the deactivation of the trigger points, although the detailed mechanism of deactivation of the active trigger points by acupuncture and moxibustion are still unclear.

### Summary points

Acupuncture activates the body's opioid analgesic mechanisms

It is proposed that the needles achieve this by stimulating polymodal receptors

Tender acupuncture points may be sensitised polymodal receptors

Polymodal receptors would respond to acupuncture and to moxibustion

### Conclusion

Acupuncture analgesia is the result of physiological and neuropharmacological processes induced by afferent inputs excited by acupuncture, and the participation of various endogenous opioids and their receptors in EAA has been widely accepted. Various nuclei and neural networks also participate in the induction of acupuncture analgesia. There are several endogenous pain inhibitory systems in the CNS, and various afferent inputs activate the systems. Acupuncture is one of the most useful procedures for activating these systems and relieving pain.

Recent archaeological investigation has demonstrated that the essential role of moxibustion therapy is recognised in establishing Chinese meridian theory. Therefore, the important role of the polymodal receptors, responsive to both acupuncture and moxibustion, is the focus of this review. The morphological and functional characteristics of polymodal receptors can explain the nature of so-called acupuncture points and trigger points. Immediate effects of acupuncture and moxibustion may be explained, at least in part, by the axon reflex via the polymodal receptor. The polymodal receptor appears to have a role in the mechanism of acupuncture and moxibustion, and to relate to so-called acupuncture points, tender points and trigger points and the activation of the endogenous pain inhibitory systems.

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