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REVIEW ARTICLE

Acupuncture Points and Their Relationship with Multireceptive Fields of Neurons

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Abstract
In Traditional Chinese Medicine, acupuncture points (APs) have been emphasized as key elements that generate the therapeutic effects of acupuncture. At the spinal cord or supraspinal level, sensory neurons located in the dorsal horn receive an extensive supply of sensory information from skin and muscle receptors through peripheral afferent nerves. The stimulated skin area that influences the activity of a spinal sensory neuron is known as the peripheral receptive field (RF) of that neuron. By considering that a particular AP location involves the activation of one or various RFs, it can be assumed that several sensory central neurons are the site of convergence of the peripheral input generated by acupuncture stimulation. However, stimulation on nonacupoint sites could also activate skin areas with RFs that have been sensitized, and they could be involved in the generation of nonspecific effects of acupuncture, as seen in clinical practice. From the latter, it is suggested that effective APs, and even nonacupoints, are associated with a particular arrangement of RFs, and their study will be useful for understanding the intrinsic mechanisms of acupuncture and for the development and identification of more efficient sites and modes of acupuncture stimulation to evoke optimal therapeutic actions.

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1. Introduction

Acupuncture is a therapeutic modality that emerged from traditional Chinese medicine (TCM). Although the World Health Organization recommends its use for the treatment of diseases [1], a systematic review and meta-analysis have questioned the real efficacy of acupuncture [2]. Contradictory results are associated with some variables that remain unsolved in acupuncture research, such as standardization and/or individualization of points to be stimulated, selection of credible control procedures, effect duration, session length, and time intervals of treatments [3]. TCM recognizes approximately 361 acupuncture points (APs) and indicates that the required therapeutic effect is evoked only by the precise stimulation of specific AP sites [4]. Until now, numerous efforts have been made to identify the clinical specificity of APs. Some evidence has pointed to the specificity of APs [5], whereas other lines of evidence do not support such notion [6,7]. Some reports have questioned the existence of APs as discrete entities [3,8], and their electrical characterization remains unsolved [9,10]. Experimental evidence has indicated that acupuncture works through the activation of particular central nervous pathways [11]. Skin and muscle sensory receptors and their axons are responsible for generating and transmitting the sensory signals from APs to first- and second-order neurons located at spinal and supraspinal levels. Dorsal horn neurons in the spinal cord receive extensive sensory inputs from peripheral skin and muscle receptors, which can be activated by electroacupuncture (EA), by several propriospinal and descending pathways and even visceral afferents [12—14]. The synaptic afferent input to a particular spinal or thalamic neuron is known as the receptive field (RF) of that neuron [14]. In this review, we analyze some neurophysiological concepts to explain the possible relationship between APs and RFs of multireceptive neurons as an example of the convergence of skin, muscle, and visceral synaptic influences exerted on individual spinal neurons [14]. We also analyzed lines of evidence suggesting that the average size of RFs could be modified by visceral pathologies. This study could yield additional information about APs and the intrinsic mechanisms of acupuncture in order to reveal more efficient sites for acupuncture stimulation to induce optimal therapeutic effects.

2. Acupoints and meridians are located close to peripheral nerves

By means of morphological studies, it has been shown that most APs are located on or adjacent to peripheral nerve trunks or branches, capillary vessels, blood vessels, lymphatic vessels, nerve receptors, nerve endings, and mast cells. The meridians correspond to trajectories of relevant deep peripheral nerves including blood vessels [15,16]. Early studies identified that myelinated and unmyelinated fibers are stimulated during acupuncture by recording the compound action potential [17]. The acupuncture-signal transmission to the central nervous system occurred through such afferent fibers [11]. Even the sensation that occurs during positioning of an acupuncture needle during treatment ("De qi sensation"), it is now generally accepted that it involves a multitude of fiber types, ranging from fast-conducting myelinated Aβ fibers of high threshold to slow-conducting unmyelinated C fibers with relatively low thresholds [18,19]. In addition, lesion of nerves, block of neuronal activity, reduction of neurotransmitter release (by pharmacologic intervention), or by lesioning the spinal cord or supraspinal regions, prevents the action of acupuncture on the function of the following systems: cardiovascular function [15,20], nociceptive or nonnociceptive pathways [11,21], immune responses [22,23], digestive system [24,25], and neuroendocrine regulation [26,27]. Therefore, the nerves within these meridians and acupoints are probably involved in the therapeutic effects of acupuncture (Figure 1).

3. RFs and multireceptive neurons

RF is generally defined as the area of the skin from which a sensory neuron can be activated by a specific stimulus [14]. Sherrington [28] was the first to use the concept of RFs to describe the area of skin from which a scratch reflex could be evoked. The properties of peripheral RFs, such as their localization, size, type of afferent fibers, and the strength of excitatory drives, are usually interpreted as indicators of the role played by central neurons in processing sensory information [29]. Sensory neurons, located in the spinal cord or in supraspinal levels, are classified according to the type of sensory modality that activates them. Neurons driven by visceral nerves, excited by the cutaneous activation of the corresponding dermatome, are considered viscerosomatic neurons [30], and they are involved in the cutaneous—visceral reflex induced by acupuncture [24,26,31]. In contrast, neurons activated by afferents from somatic sensory receptors, but not by visceral afferents, are known as somatic neurons [30]. A subclassification corresponds to neurons that respond to both noxious and nonnoxious inputs and participates in the antinociceptive effect exerted by acupuncture on somatic pain [11]. Another characteristic of a particular RF is that it shows a change in response owing to excitatory and/or inhibitory influences from segmental or descending pathways [14,32]. In addition, RF could be modified by experience or by injury to sensory nerves.

There are several other groups of neurons that receive synaptic inputs from receptors responding to different skin sense modalities (i.e., from light touch to noxious deep pressure), which are called "multireceptive neurons" [14]. Visceral and skin RF inputs converge on the same spinal viscerosomatic neuron [14], even at the supraspinal level [33]. This converging somatic and visceral influence into neurons allows peripheral stimulation to modulate the excitability and firing patterns of neural networks [11,17]. As an example, visceral or somatic nociceptive inputs arrive to multireceptive spinal neurons, which are inhibited by tactile, heat, or noxious conditioning stimuli applied to the skin, viscera, and/or muscle pathways [30,34,35], or by activation of descending pathways involved in analgesia, such as the raphespinal, reticulospinal, or ceruleospinal tracts [17,36].

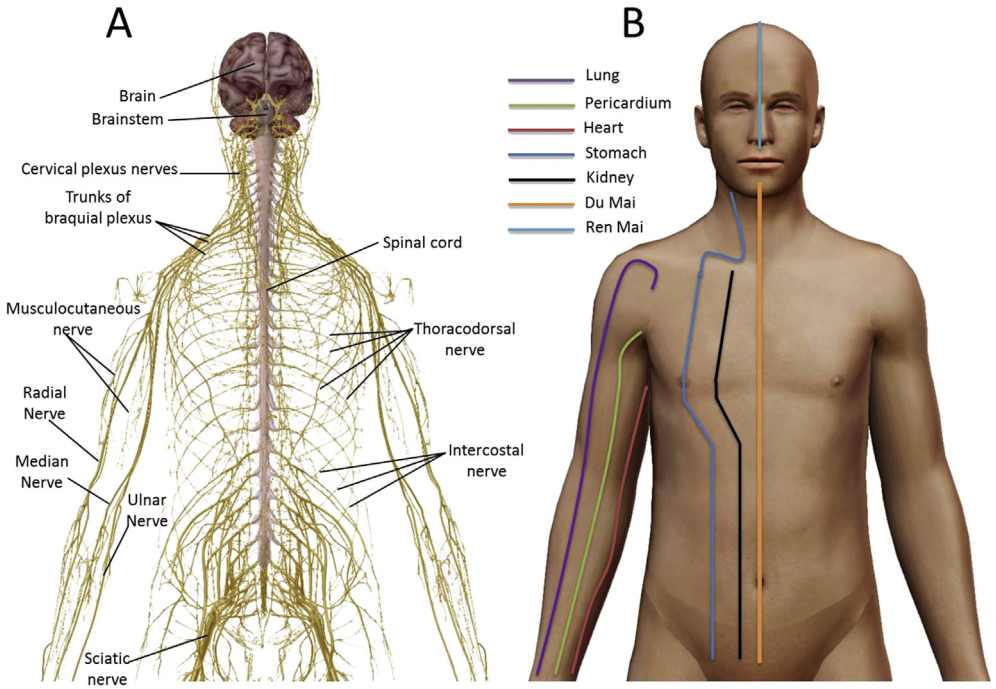

Figure 1 Relations between (A) peripheral nerves with (B) some channels of acupuncture.

4. Relation of acupoints with multireceptive neurons

In TCM, acupoints are located on body surfaces where the Qi of meridians and internal organs is streaming. According to the TCM theory, the therapeutic effects of AP stimulation work through 12 principal meridians that represent channels, where Qi flows and connect with various internal organs. The abnormal flow of Qi in a meridian is related to disease, and its natural flow can be restored by stimulation of appropriate APs [4].

The convergence of sensory inputs on multireceptive spinal neurons could explain some relationships between internal organs and APs [37,38]. It has been shown that acupuncture exerts its therapeutic effects through the modulation of neuronal activity at the level of the dorsal root ganglion [11,30,39], spinal cord [38,40,41], trigeminal nucleus [42], thalamus [34], and brain [17], where acupuncture might inhibit the neuronal discharges induced by somatic and visceral pain [11]. Multireceptive neurons could be the target of converging input from acupuncture stimulation to reduce visceral pain (Figure 2). Convergent inputs from visceral and somatic territories have been reported at the level of the dorsolateral medulla [41,43,44], solitary nucleus [45,46], spinal cord [46], thalamus [47], and midbrain periaqueductal gray [33]; acupuncture also evokes neuronal responses in those areas [11,17]. In this way, the interrelation between body surface sensory receptors, multireceptive neurons, and internal organ receptors, and/or between meridians and internal organs may have certain common neurophysiological and morphological basis.

An important mechanism demonstrating that it is produced by injury of viscera structures is the long-term sensitization that results in the progressive amplification of the nociceptive response (Figure 3). As an example, central sensitization is associated with an expansion of the RF of various central neurons, resulting in a larger topographic distribution of pain [35,48,49]. In addition, a repeated nociceptive input from muscle or stimulation of peripheral RF of spinal neurons results in an expansion of the central RF [49]. As a result of the colorectal inflammatory reaction, the average size of the RF of multireceptive neurons increased as the visceral inflammatory reaction intensified. Multiple distending of the esophagus by means of an air sac results in the expansion of the receptor field of dorsal horn neurons in T2—T4 [50]. In this way, the output of multireceptive neurons should be understood in ample dynamic terms because the size of the peripheral field of individual neurons may change as a result of neuronal plasticity.

4.1. Do acupoints expand under pathological conditions such as dynamic RFs?

Recent lines of evidence showed that when internal organs are under pathological conditions, acupoints become more sensitive [35], and the size of acupoints varies according to visceral alterations [48,51]. A study in dysmenorrheal patients found that the most sensitive points were divergent from the standard location of the *Diji* (SP 8) acupoint, which indicates that the location of the *Diji* area in pathological states is different from the standardized location [52]. Ben and collaborators [53] investigated the sensitization of human skin points along meridians related to visceral disease by using the pressure-pain threshold as an indicator. Their results showed the existence of pain-sensitive points on the abdomen and back regions of

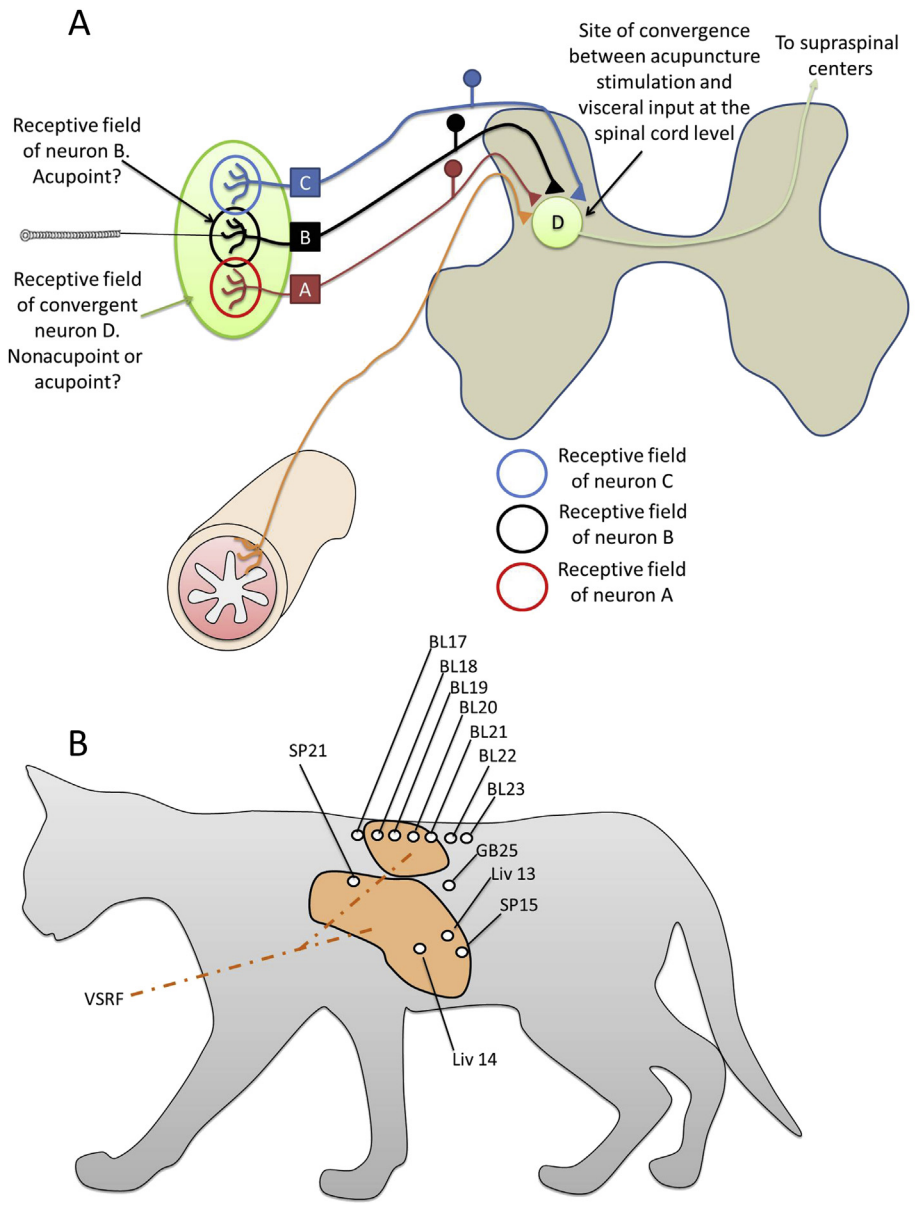

Figure 2 Receptive fields and acupoints. (A) Arrangement of somatic and visceral receptive fields in the periphery. (B) Distribution of acupoints on viscerosomatic receptive field (VSRF). BL = bladder; GB = gall bladder; Liv = liver; SP = spleen. See text for further details.

patients with gastric ulcer [53]. In addition, some morphological studies have shown that under the inflammatory state, sick organs can promote the extravasation of Evans Blue (EB) on the body surface [54—56]. In rats with ovarian inflammation, extravasated EB points are mainly distributed around the "Guanyuan (RN4)"—"Uterus" area and the "Shenshu (BL23)"—"Mingmen (DU4)" area [57,58]. In rats with acute gastric mucosa inflammation, the extravasated EB points are distributed along the nerve segments and highly coincide with "Pishu (BL20)," "Shenshu (BL23)," and nearby acupoints [55]. But extravasation of EB points is rarely observed in healthy rats. All these results raised the concept of "acupoint sensitization" [57], which indicates that when the organs change from the healthy state to the pathological state, acupoints shift from the silent state model to the sensitized state model. Another emergent concept is "dynamic states of APs" deeming that the size and function of acupoints are not in a stable state, but are in a changing and dynamic one (Figure 4). The function and size of APs will vary along with the state of the body, particularly with the function of a specific internal organ [58,59]. Therefore, in pathological conditions, the diagnostic and therapeutic effects of acupoints on visceral diseases are enhanced (Figure 4).

By means of electrophysiological approaches, additional experimental evidence has been obtained to support the proposition that the area and sensitization of the RF of particular acupoints changed when internal organs are under pathological conditions [60]. Visceral inflammation facilitates the subnucleus reticularis dorsalis neuron

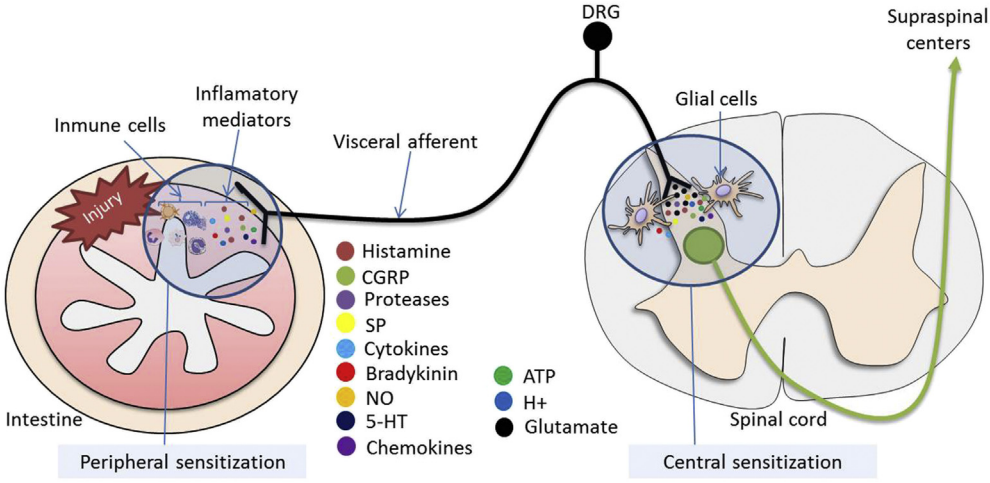

Figure 3 Peripheral and central sensitization in the afferent visceral nerves and spinal cord. Wide dynamic range (WDR) neurons (green) activated by visceral inflammation at the intestine level. Inflammatory mediators are released through immune, epithelial, neuronal and glial cells. ATP = adenosine triphosphate; CGRP = galcitinin gene related peptide; DRG = dorsal root ganglion; 5-HT = 5-hydroxytryptamine; H^+ = hydrogen ions; NO = nitric oxide; SP = substance P.

responses to acupoint stimulation. Yu and coworkers [60] showed an increment in the activity of wide dynamic range neurons provoked by EA when an increment occurred in visceral nociception. In this way, the size and function of acupoints comply with the functionality of the internal organs, and the sensitivity of acupoints changed according to the malfunction of internal organs (Figure 4).

4.2. Clinical implications of acupoint sensitization

Lines of evidence about the RF expansion of neurons could explain the observation, under clinical conditions, that stimulation of areas adjacent to AP (nonacupoints) would evoke therapeutic effects. Those effects could also be interpreted as unspecific effects provoked by acupuncture, as suggested previously by Lund and colleagues [61]. As an example, for chronic pain patients with sensitization of peripheral and spinal cord neurons, their response to acupuncture is increased, whereby a slight stimulation of the skin may have an effect as strong as the acupuncture itself [61,62]. According to Lundeberg and Lund [62], control procedures with light needling of the skin and/or needling away from the target treated site (pain area) in patients with central sensitization, may have effects equivalent to needling within the treatment site. In other words, a control procedure with needling in a nearby myotome may have similar effects as needling within the affected myotome. In addition, by considering that some RFs are associated with acupoints and nonacupoints, EA stimulation of such RFs ("sham acupuncture") evoked a therapeutic effect that could be considered an unspecific action of EA [62].

5. APs as RFs and the meridian theory

The proposition that acupuncture is an RF dynamic process is not in conflict with the meridian theory. Most skin RFs of thalamic neurons responding to visceral nociceptors are closely located along the stomach meridian. Sato and colleagues [63–65] and Uchida et al [66] performed several studies using acupuncture-like stimulation (ALS) in which the acupuncture needles are placed extensively throughout the body RFs of experimental animals. They observed that ALS provokes alterations in bladder contraction [63], gastric motility [64], sympathoadrenal medullary function [65], heart rate [66], and immune organs [65]. As an example, ALS applied at the perineal area and underlying muscles (associated with Ren, Du, and Kidney meridians) inhibited the rhythmic micturition contractions of the urinary bladder and the rhythmic burst discharges recorded in vesical pelvic efferent nerves. However, ALS applied to the face, neck, forelimb, chest, abdomen, back, and hind limb areas of anesthetized rats was not able to produce such effects [64]. Other studies reported that ALS applied in regions of the abdomen or hind limbs increased the secretion of catecholamines and nerve activity (spinal afferent nerves ipsilateral to the stimulated site at the T9, T10, T11, and T12 levels and femoral and sciatic nerves), but abdominal stimulation (associated with the segmental territory of the stomach or spleen meridian) produced larger responses than those evoked by hind limb stimulation [65]. It has also been shown that ALS applied on the abdomen (in a region associated with the stomach meridian line) provoked a reduction of gastric motility [31,65]. Viscerosomatic neurons in the thoracic spinal cord receive the synaptic actions of splanchnic afferents from the 11 thoracic dermatomes but, in addition, they have a cutaneous RF in the costal region, extending over two to five intercostal spaces but restricted, in a dorsoventral direction, to approximately one-third to one-fourth of the total extent of the dermatome [30]. Such a trajectory is superposed with acupoints associated to spleen, bladder, and liver meridians (Figure 1). Furthermore, a subset of acupoint locations coincides with RFs (Figure 1B). Li et al [67] found that RFs of both A and C fibers are concentrated either at sites of APs or on the route of meridian channels, indicating that the distribution of RFs was closely related to

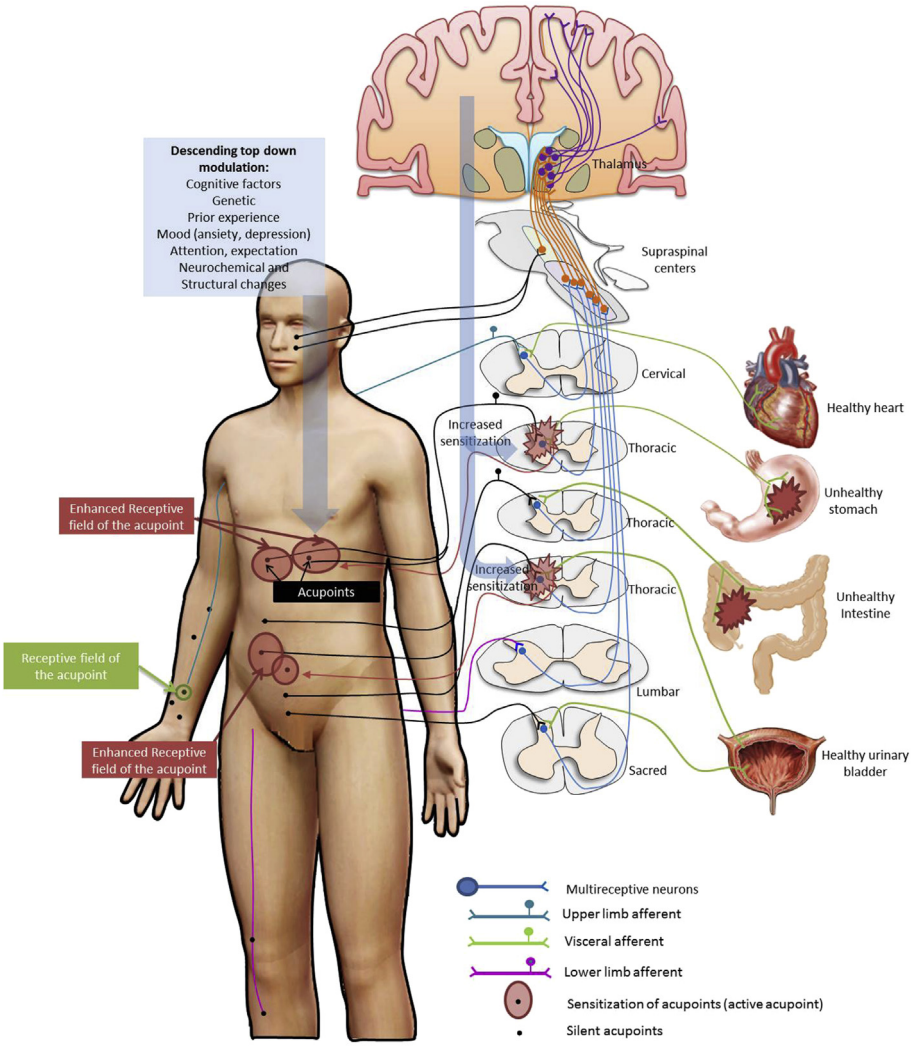

Figure 4 Summary of the relations between acupuncture points (●) and multireceptive field neurons (lines in blue). Dorsal horn neurons in the spinal cord receive extensive sensory inputs from peripheral skin and visceral afferents, which in turn send axonal branches to supraspinal and central nuclei. Stomach and colon under inflammatory conditions increase the sensory input to spinal cord neurons, which in turn send axonal projections to supraspinal or peripheral cutaneous acupoints areas by reflex mechanisms. In addition, the enhanced receptive field of an acupoint results from changes in the visceral and spinal cord sensitization, and the acupoint shifts from the silent state model to the sensitized state model. Receptive fields of acupoints are also under descending influences, which are dependent on the individual conditions of the organism.

meridians. Pain-sensitive points located at the abdomen and back regions of patients suffering from gastric ulcer were associated to acupoints situated on the stomach meridian [53]. In this sense, the meridian theory would also be established by observations of clinical phenomena in visceral diseases of bandlike distribution of sensitive skin associated with RFs of spinal neurons.

6. Acupoints outside of meridians

Studies conducted in human volunteers also demonstrated that acupuncture, at skin points relatively away from a particular meridian, may generate effects that are comparable to acupuncture within the meridian, and they could be associated to the sensitization phenomenon of acupoints [68,69]. As pointed out previously, trigger or tender points are frequently found in visceral illnesses, including chronic visceral pain. Trigger points are the focal skin areas where allodynia takes place, and they can be switched "on" or "off" from the classical meridian routes. Melzack and collaborators [70] made a comprehensive description of such trigger points about 30 years ago. Considerable evidence indicated that stimulation of trigger points by needling, intense cold, point injection [71] or transcutaneous nerve stimulation [72] may relieve pain. Furthermore, it is not clear whether the possible sensitive sites on the body surface, associated to visceral pain, are related to acupoints, in particular to the Ah-shi acupoint.

7. Conclusion and future directions

A receptive field is defined as the area of skin from which the activity of a neuron can be influenced. By considering that a subset of RFs conforms to a particular AP, it is

proposed that different classes of neurons are sites of convergence of the afferent input generated by acupuncture stimulation. Even the specificity of EA stimulation to provoke spinal cord dorsum potentials is suggested to be primarily related to peripheral nerve routes [73]. In spite of that, activation of other skin areas with active RFs but different from those exerting a particular acupuncture action (nonacupoints) explains the occurrence of nonspecific effects provoked by acupuncture procedures, as reported in clinical trials. On the other side, the effects of acupuncture need to be examined from the perspective of RF, in which properties of the RF must be further considered. For example, the segmental RF of multireceptive neurons is generally located on the skin and is made up of an excitatory field or an inhibitory field. In that sense, peripheral influences could be both excitatory and inhibitory, and pain can be relieved by reinforced segmental inhibitory controls through electrical stimulation by EA or other empirical physical means.

Finally, insertion of an acupuncture needle into a designated point on the body surface produces a stimulus that evokes the activation of multiple central neuronal pathways [21,31]. An optimal response to acupuncture might be a consequence of the efficiency and specificity of the stimulation site and activation of particular pathways in the central nervous system. Precise identification of AP became challenging because the size and location of RFs for multireceptive neurons could be increased or modified by changes in the physiological condition of the individual (Figure 4); even the response of spinal dorsal horn neurons to a particular RF would change as a result of excitatory and inhibitory influences exerted by segmental, propriospinal, or descending processes impinging on them at a particular time. Consequently, in clinical practice, each patient could have sites of acupuncture stimulation that do not correspond strictly with traditional APs, probably because they are associated with RFs varying dynamically in time and magnitude, according to the general physiological state of the individual (Figure 4). Considering AP stimulation as a dynamic and complex process might help us understand the different degrees of acupoint specificity observed during diverse clinical conditions. From a neurophysiological perspective, APs considered as dynamic RFs could be of considerable importance for the characterization of acupuncture actions and for the development and/or improvement of acupuncture procedures to obtain optimal therapeutic treatments.

Disclosure statement

None.

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