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Significance of pleasant touch and state-of-the-art neuroscience technologies in acupuncture research

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An article entitled "Molecular and neural basis of pleasant touch sensation" was published in the top journal Science last year. This research describes the neural circuit of pleasant touch from the skin to the spinal cord[1]. Acupuncture and other somatic stimulation therapies also induce comfortable and enjoyable experiences. In the former studies, the mechanisms of these experiences in the brain are discussed. The paper published in *Science* gave us a novel perspective on the neural circuit of pleasant touch sensation from the skin to the spinal cord. In the following four sections, we would like to give our thoughts about how the paper would affect acupuncture research.

Role of pleasant touch in acupoints and somatic stimulation therapies

In the ancient Chinese medicine book *Inner cannon of Huangdi* (huáng dì nèi jīng, 黄帝内经), acupoints miraculously affected patients: "feel relieved and comfortable when pressed." The theory of acupoints originates from *Miraculous Pivot* (Líng shū jīng, 灵枢经): "The site of pain is Shu (acupoint)." *Miraculous Pivot* (Líng shū jīng, 灵枢经) kept a record: when Shu (acupoint) was pressed, body pain was relieved. Sun Simiao stated in *Thousand-GoldenPrescriptions* (bèi jí qiān jīn yào fāng, 备急千金要方) that when the patients have pain or diseases, press the body. If the right site is pressed (acupoint or not), the patients would say "Ah~Shi~" when they felt comfortable or painful. These Ashi points could relieve pain or diseases when acupuncture, moxibustion, or other somatic stimulations worked. From the above descriptions of Ashi points or acupoints, an important effect of pressing at the sites was comfort and relief, and painful sensation at the sites. These unusual feelings of the acupoints or Ashi points of the body are called sensitization of acupoints. They are somatic reflection of the pathophysiological conditions of the visceral or other body areas.

Pressing at these sites is very important and well-carried out before many somatic stimulation therapies, especially in acupuncture practitioners. This kind of comfortable or relieved feeling is provoked when the right site(traditional acupoint or trigger point) is pressed. In addition, a positive valence of emotion-trust between patients and doctors is needed. The molecular circuit of these effects can be explained by somatic stimulations, such as acupuncture, which can enhance the neurotransmitters and hormones secreted by the central nervous system, regulating body functions, such as oxytocin, dopamine, serotonin, and endorphins[2–5]. From the periphery, this comfort and relief was partly achieved by pleasant touch. The sensations of touch are classified as discriminative and pleasant. Discriminative touch senses the physical characteristics of the touch stimuli, for example, the pressure, texture, speed, or shape, which are conducted by fast glutamate Aβ low-threshold mechanical receptors (LTMRs). A pleasant touch sensation reflects the positive emotions or rewards of touch stimuli. C-tactile (CT) afferents transmit the pleasantness of touch in humans[6]. In animals, C-LTMRs in the skin transmit pleasant touch sensation[7].

Somatic stimulation of specific body sites initiates a fast discriminative touch sensation. The touch sensation locates the stimulation sites and produces the *de qi* sensation of acupuncture and other somatic stimulations. *De qi* feelings, such as soreness, numbness, heaviness, and distension, are mainly produced in the deep muscle layers of the stimulation site. Pleasant touch is also induced to provide comfort and well-being to the subjects. In our study, we used the *in vivo* intracellular electrophysiological method of recording the dorsal root ganglion (DRG) soma in anesthetized rats and found that C-LTMRs which transmit pleasant touch, could be activated by different intensites of mechanical touch , different angle of acupuncture manipulation and heat stimulation. C-LTMRs had a lower mechanical threshold in the receptive field compared to C high-threshold mechanical receptors (C-HTMRs) (Figure 1). The C-LTMRs and C-HTMRs reacted to different angles of manual acupuncture manipulation of the receptive field (Figure 2); however, C-LTMRs had no obvious linear relationship with the temperature increment in the receptive field compared to C-HTMRs (Figure 3) (unpublished data).

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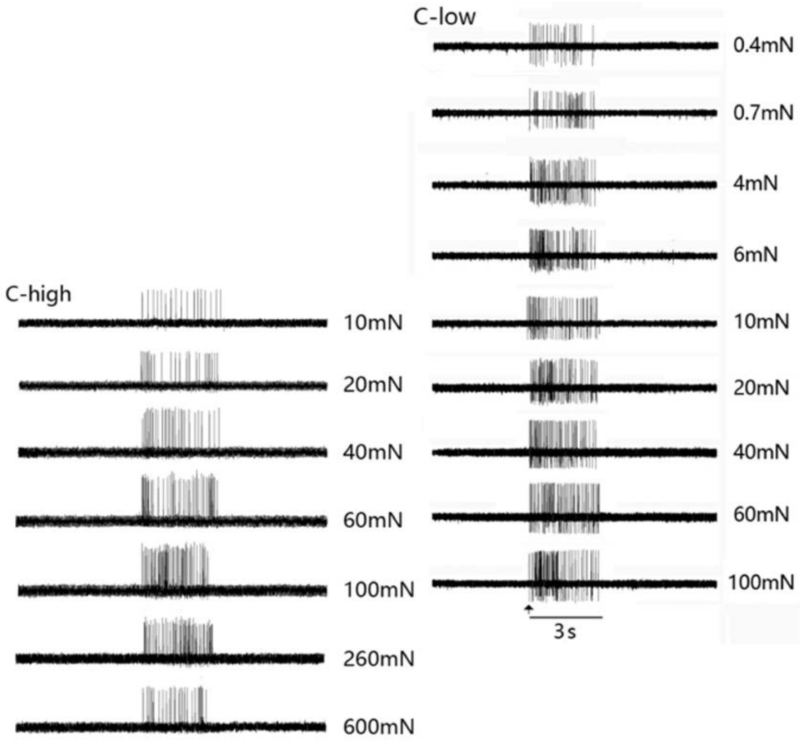

Figure 1. Activities of one C-LTMR and C-HTMR are induced by different intensities of mechanical stimulation on the receptive field. C-HTMR: C high-threshold mechanical receptor; C-LTMR: C low-threshold mechanical receptor.

PROK2-PROKR2 spinal neural circuit of pleasant touch sensation

Liu et al. explored the spinal neural circuit of pleasant touch using subtype-specific ablation of spinal dorsal horn neurons, optogenetics, electrophysiology, and rabies virus-based transsynaptic tracing [1]. Prokineticin receptor 2 (PROKR2) neurons were mostly distributed in lamina II of the spinal cord of the reporter line: PROKR2-GFP mice. After intersectional genetic ablation of the spinal subpopulation-PROKR2 neurons, pleasant touch-induced conditioned place preference (PT-CPP) was lost. No abnormal pain or itch behavior was observed in spinal PROKR2 neuron-ablated mice. Optogenetic stimulation of the spinal cord in PROKR2-ChR2 mice also showed a real-time preference for the stimuli chamber. After these two experiments, the PROKR2 neurons in the spinal dorsal horn transmitted the positive valence of stroking through loss-of-function and gain-of-function experiments.

Liu et al. identified that the peripheral inputs of PROKR2 neurons were predominantly mono- and polysynaptic C fibers with patch clamps in the parasagittal section of spinal slices obtained from PROKR2-GFP mice. Spinal PROKR2 neurons vigorously reacted to the brush with *in vivo* extracellular recordings of PROKR2-ChR2 mice. After rabies virus-mediated retrograde tracing in PROKR2-Cre mice, they identified that up to 70% of the input neurons in DRGs project to spinal PROKR2 neurons co-labeled with Prok2. Liu et al. further developed Prok2 conditional knockout (CKO) mice by breeding floxed Prok2 mice with Nav1.8-Cre mice. In Prok2 CKO mice, Prok2 was knocked out in Nav1.8-Cre positive neurons of the DRGs. No PT-CPP was induced in Prok2 CKO mice. The neuropeptide Prok2 from C-type neurons of the DRGs is indispensable for pleasant touch sensation [1].

State-of-the-art technologies in neuroscience help acupuncture research

The methods of genetic strategies, including genetically engineered mice, genetically edited virus vectors, and optogenetic manipulations on certain subtypes of neurons applied in this study are state-of-the-art technologies in neuroscience research. These genetic manipulating technologies have provided further specific tools for studying the afferent and efferent pathways of somatic stimulation both in the nervous system and target organs[8–9]. Two studies from Ma Qiufu Lab identified the neuroanatomical basis of acupuncture. A mechanism of acupuncture regulation of body physiology at distant sites is somatosensory autonomic reflexes. Studies from Ma Lab proved that PROKR2 Cre-marked sensory fibers innervating the hindlimb fascia, but not the abdominal fascia, were crucial for driving the vagal-adrenal axis[4]. They also found that low-intensity electroacupuncture (ES) in the hindlimb regions drove the vagal-adrenal axis, producing anti-inflammatory effects that depend on neuropeptide Y (NPY) + adrenal chromaffin cells. However, high-intensity ES in the abdominal regions activates NPY + splenic noradrenergic neurons *via* the spinal-sympathetic axis[9]. In these two studies, the subpopulations of the afferent and efferent pathways of ES were manipulated using genetic engineering strategies. For example, specific ablation or

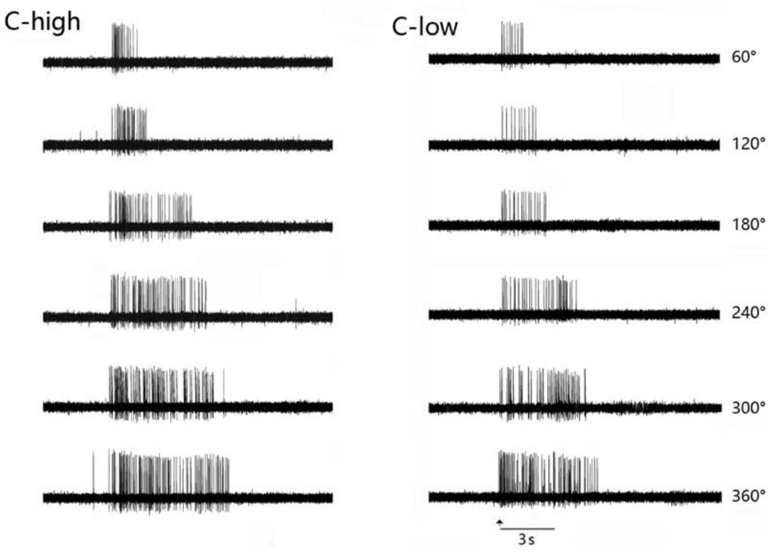

Figure 2. Activities of one C-LTMR and C-HTMR are induced by different angles of acupuncture stimulation on the receptive field. C-HTMR: C high-threshold mechanical receptor; C-LTMR: C low-threshold mechanical receptor.

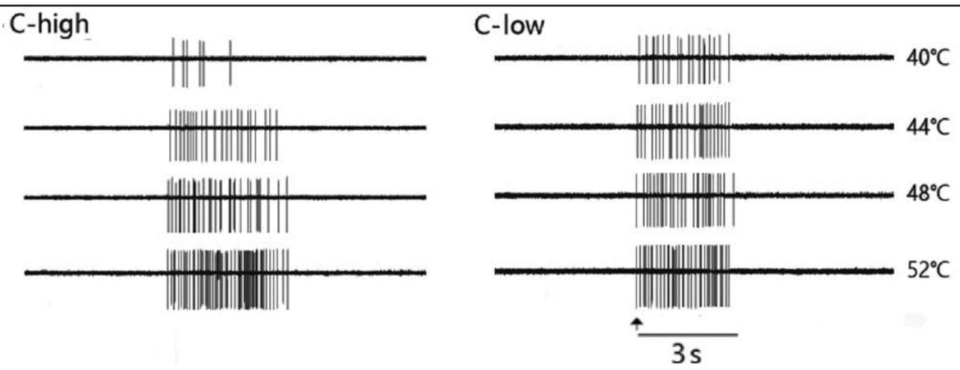

Figure 3. Activities of one C-LTMR and C-HTMR are induced by different temperatures of moxibustion stimulation on the receptive field. C-HTMR: C high-threshold mechanical receptor; C-LTMR: C low-threshold mechanical receptor.

optogenetic stimulation of DRG PROKR2 Cre-marked neurons without affecting PROKR2 Cre expression in other nervous systems, and an intersectional genetic strategy to manipulate sympathetic cells expressing NPY in the sympathetic ganglia and/or adrenal glands. These two studies attempted to identify the specificity and intensity dependence of somatic stimulation with specific afferent and efferent neural pathways under systemic inflammation conditions.

Behavioral paradigm of pleasant touch in awake freely moving mice

Iiu et al. developed a novel pleasant-touch behavioral paradigm in mice (PT-CPP) (Figure 4). In this behavioral paradigm, soft brush-induced stroking was applied on the back of the mice, and the stroking speed that produced the positive valence of the mice was 18 to 22 cm/s (2–3 Hz/s), moving from the nape to the lumbar enlargement area or vice versa. The stimulation period lasted for 1 minute, with intervals of 5 minutes, with three circles per day. The mice showed a preference for the stroking chamber after eight alternative sessions. In particular, these kinds of stimuli will be conducted in freely moving awake mice, similar to somatic treatment in the clinic. Mice are a popular experimental animal because of development of mouse genetic engineering, which provides more genetic manipulation tools for acupuncture research[8–9]. This paradigm of somatic stimulus in freely moving awake mice has provided many insights into the mechanisms of somatic stimuli. The central nervous system pathways of pleasant touch and the effect of somatic stimuli will be further explored because of the brush somatic stimulation paradigm in awake mice.

This stroking-behavioral paradigm can be further developed into many somatic stimulation paradigms. The stimulation force can be increased to mimic massage. The site of stimulation can be more limited than the entire back stimulation, for example, the nape, upper back, or lower back. These behavioral paradigms will further help to study the effects and neural biological

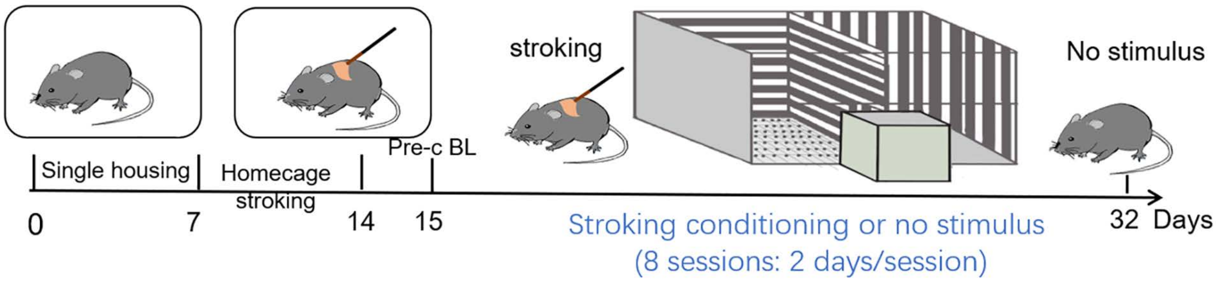

Figure 4. Pleasant touch conditioned place preference (PT-CPP).

mechanisms of somatic stimulation in different pathological conditions.

Conclusions

The pleasant touch-transmitting neural circuit may be involved in the effect of acupuncture-like somatic stimulation therapies and may have a real therapeutic effect on "comfort". From the clinical effect of traditional acupoints, pressing leads to comfort. Acupuncture and moxibustion, especially massage, scraping, cupping, and other therapies in the external treatment of traditional Chinese medicine might be involved in the participation of pleasant touch spinal pathways. The use of "pleasant" sensation as a carrier for acupuncture-moxibustion, massage, and acupoint research will help elucidate the intrinsic characteristics of acupoints and the mechanism of somatic stimulation therapies such as acupuncture and moxibustion. It will deepen the understanding of somatic stimulation therapy, promote the progress of acupuncture and moxibustion, and further improve its clinical efficacy.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Bing Zhu and Kun Liu conceived the idea of this article, Kun Liu drafted the manuscript. Bing Zhu and Kun Liu modified the manuscript.

Ethical approval of studies and informed consent

There is no human or animal studies in this article and informed consent is not required.

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References

[1] Liu BL, Qiao LN, Liu K, et al. Molecular and neural basis of pleasant touch sensation. *Science* 2022;376:483–491.
[2] Moles A, Kieffer BL, D'Amato FR. Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. *Science* 2004;304:1983–1986.
[3] Pecina S, Smith KS, Berridge KC. Hedonic hot spots in the brain. *Neuroscientist* 2006;12:500–511.
[4] Uvanas-Moberg K, Arn I, Magnusson D. The psychobiology of emotion: the role of the oxytocinergic system. *Int J Behav Med* 2005;12:59–65.
[5] Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional and behavioural control processes. *Trends Cogn Sci* 2008;12:31–40.
[6] Löken LS, Wessberg J, Morrison I, et al. Coding of pleasant touch by unmyelinated afferents in humans. *Nat Neurosci* 2009;12(5):547–548.
[7] Vrontou S, Wong AM, Rau KK, et al. Genetic identification of C fibres that detect massage-like stroking of hairy skin in vivo. *Nature* 2013;493(7434):669–673.
[8] Liu SB, Wang ZF, Su YS, et al. A neuroanatomical basis for electroacupuncture to drive the vagal-adrenal axis. *Nature* 2021;598(7882):641–645.
[9] Liu SB, Wang ZF, Su YS, et al. Somatotopic organization and intensity dependence in driving distinct NPY-expressing sympathetic pathways by electroacupuncture. *Neuron* 2020;108(3):436–450.e7.

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