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When sng meets acupuncture -- a paradigm-shift biomarker for translational research

Wei-Zen Sun [a,b], Chih-Cheng Chen [c,d,e,*], Jaung-Geng Lin [f,**]

[a] Department of Anesthesiology, Cathay General Hospital, Taipei, Taiwan
[b] Health Science & Wellness Center, National Taiwan University, Taipei, Taiwan
[c] Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
[d] Neuroscience Program of Academia Sinica, Academia Sinica, Taipei, Taiwan
[e] Graduate Institute of Acupuncture Science, China Medical University, Taichung, Taiwan
[f] Chinese Medicine Research Center, China Medical University, Taichung, Taiwan

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ABSTRACT

The sensation of sng (pronounced/səŋ/, the Romanization form of 痠or soreness in Taiwanese Southern Min) associated with *de qi*, a composite of unique sensations, is a novel phenotype for acupoint stimulation. It is perceived by test participants but also by experienced practitioners as a sensation of "taking the bait" (by fish when fishing), a characteristic heavy and tight sensation from the needle. Here, we propose that sng is a powerful biomarker for *de qi* associated with successful manual acupuncture. Sngception (sng-ception), a specific somatosensory function of acid-sensation or tether-mode mechano-sensation, may serve as the ideal molecular and physiological link between sng perception and needle manipulation (e.g., lifting, thrusting, and twisting). To explain how manual acupuncture can induce *de qi*, we constructed a hypothetical model of manual needling-driven sngception. In acupoints (e.g., ST36), an acupuncture needle can easily stick to extracellular matrix (ECM) proteins (e.g., fibronectin and laminin). While the acupuncture needle is manually twisted, it mingles with ECM and delivers a pulling force to ECM-tethered mechanically sensitive ion channels (e.g., acid-sensing ion channels) on somatosensory nerves to induce sngception. The concept of sng and sngception represents an emerging field for research into the peripheral mechanisms of acupuncture.

1. *De qi* is a cornerstone in acupuncture research

The soreness sensation associated with *de qi*, a composite of unique sensations experienced during acupuncture, is a novel phenotype in acupoint stimulation. It is perceived by test participants as well as experienced practitioners as a sensation of "taking the bait" (by fish when fishing), a characteristic heavy and tight sensation from the needle.[1] Cumulating evidence from traditional research and clinical experience has supported *de qi* as a prerequisite for any clinical therapeutic effect.[2–4] In humans, outcomes were more favorable with a stronger intensity of *de qi* with the needle and transcutaneous electrical nerve stimulation.[5,6] In our animal study, we further demonstrated that electroacupuncture to the ST36 acupoint could prolong tail-flick latency depending on intensity.[7] However, the most challenging task in any acupuncture study design is how to remove the cognitive bias associated with treatment-induced discomfort and placebo expectation. In a systemic review, Madsen et al. found that a meaningful analgesic effect couldn't be distinguished from bias, and thus casual needling, even without any *de qi*, could reduce pain as a result of the psychological impact of the treatment ritual.[8] Recently, Kim et al. found no significant differences in levels of 36 serum biomarkers before and after sham and verum acupuncture needling.[9]

2. Biomarkers are vital for translational research in pain management

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue

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* Corresponding author. Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan.
** Corresponding author.
E-mail addresses: chih@ibms.sinica.edu.tw (C.-C. Chen), jglin@mail.cmu.edu.tw (J.-G. Lin).

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damage (revised International Association of the Study of Pain definition of pain, 2020).[10] From the perspective of clinical research, translational biomarkers are essential to identify the impact of acupuncture stimulation on the human body before a clinical effect is evident.[11] Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention".[12] Biomarkers are divided into 3 general classes: target biomarkers, mechanism biomarkers and disease biomarkers. Numerous histochemical and electrophysiological biomarkers have been reported to measure acupuncture-induced responses. Electrophysiological techniques (e.g., electroencephalography-based density spectral arrays) provide a temporal and spatial relationship of neural activities.[13] Recently, we found functional near-infrared spectroscopy as a useful, non-invasive imaging tool to detect levels of oxygenated and deoxygenated hemes during local muscular and brain activity during acupuncture stimulation.[14] More recently, neuroimaging techniques (e.g., positron emission tomography,[15] magnetoencephalography,[16] and functional MRI[17]) have been useful in detecting humans the brain structure–activity relationship. Although these mechanistic biomarkers are useful in studying pain and its modulatory pathways under normal conditions, they are not practical and acceptable in the clinical settings of acupuncture practice. Thus, we need a translational biomarker that can be used to continuously monitor the changes in local muscular response during acupuncture.

3. Biomarker for *de qi*

Measuring the analgesic response remains a critical challenge in both animal and clinical studies.[18] Most clinical endpoints were designed to compare the verbal and/or visual rated pain intensity from conscious and oriented participants. Recording verbal and/or behavioral responses is difficult among people with poor communication associated with extreme age and cognitive deficits (e.g., dementia, aphasia, delirium and under general anesthesia). In a previous study, we found that intraoperative electroacupuncture stimulation was not attenuated by general anesthesia, which led to an effective reduction in postoperative pain and nausea/vomiting.[19] A growing concern is the unethical fear and distress during intense stimulation to an awake animal. In a minimal stress model, we suppressed behavioral and psychological distress in rats to count intensity-dependent leg withdrawal reflex in response to graded stimulation of electroacupuncture.[20] However, regardless of the long-held advocacy for *de qi*, there is no objective, quantitative biomarker to measure it in either animal or clinical research.

To distinguish needling-induced analgesia from the emotional distress associated with treatment-induced discomfort, we propose that a reliable biomarker with a phenotype characteristic should be measured under general anesthesia. In an earlier study, Agarwal-Kozlowski et al. demonstrated an immediate vasodilation response after needling in an acupoint but not in a non-acupoint.[21] Although microcirculation is increased after *de qi*, mechanical stimulating the acupoints could open ion channels, thereby triggering the release of neurotransmitters, which in turn increase regional blood flow and simultaneously evoke a painful sensation.[22] Thus, local neurogenic vasodilation and segmental nociception could occur as a result of the mechanical stimulation to acupoints, which also manifests as the typical acid (or soreness)-like sensation triggered by massage or ultrasound stimulation.

4. Sng and sngception

While an acupuncture needle mechanically lifts, thrusts, and twists the acupoint, a *de qi* sensation can be achieved as a sign of successful analgesia.[23–25] Acupuncture *de qi* is a complex somatosensory sensation. The common and distinctive characteristics include soreness, numbness, fullness, pain, and many other sensory experiences.[26,27] Despite several ways to validate *de qi*, sng (pronounced/səŋ/, the Romanization form of 痠or soreness in Taiwanese Southern Min) may be the most prominent.[24,25] We previously proposed a sngception theory to address the somatosensory function of acid sensation and/or mechanical stimuli and defined sng as the corresponding perception.[28] From neurobiological aspects, sngception (acid sensation) is distinguishable from nociception, because acid sensation can be pronociceptive or non-nociceptive, or even antinociceptive.[29] In fact, more than 70 % of somatosensory neurons are acid-sensitive, and many (e.g., proprioceptors) are not nociceptors.[29,30]

Clinically, we have demonstrated that sng (or soreness) and pain are 2 distinct symptoms in patients with fibromyalgia and degenerative spine diseases.[31–33] However, soreness is defined as pain in the English language and thus not suitable to represent the acid-like perception of *de qi*. To avoid confusion and facilitate scientific progress, we propose using sng to replace soreness in response to sngception. The sng of *de qi* could be a practical biomarker measuring successful analgesia during acupuncture. Although how the acupuncture-driven sng works is still not known, proton-sensing ion channels such as acid-sensing ion channels (ASICs) involved in antinociceptive acid signaling might be a possible peripheral mechanism to link the mechanical needling and sng of *de qi*. Of note, during tissue acidosis, proton-sensing ion channels of ASIC1b, ASIC3, and transient receptor potential V1 (TRPV1) were pronociceptive, whereas ASIC1a was antinociceptive in a mouse model of fibromyalgia induced by intramuscular acidosis.[34–37] An unsolved question is how mechanical stimuli induced by needle lifting, thrusting, and twisting can activate antinociceptive proton-sensing ion channels.

5. Searching for mechanically sensitive ion channels responding to needle lifting, thrusting, and twisting

Although forceful needle lifting, thrusting, and twisting are the most common practices to induce *de qi*, the underlying mechanism is still unclear. There are at least 3 knowledge gaps between the unique traditional maneuvers and physiological explanation that remain to be resolved: (1) whether the acupoints are enriched with acid-sensitive nerves; (2) how needle lifting, thrusting, or twisting can activate nerves of acupoints; and (3) how the needle-driven mechanotransduction can lead to sng perception. To fill in the knowledge gaps, we propose a "manual needling-driven sngception theory" for a wholistic explanation of how needle lifting, thrusting, and twisting selectively activate mechanically sensitive ion channels expressed in acid-sensitive somatosensory nerves (Fig. 1).

From a biophysics aspect, mechanically sensitive ion channels can be gated via 2 different models: (1) a bilayer model, in which ion channels are activated via alteration of membrane tension (e.g., membrane deformation due to osmotic stress), and (2) a tether model, in which ion channels are activated by tethered elements of extracellular matrix (ECM) proteins and/or intracellular cytoskeletons to transmit the force.[38] Previous studies had largely used different mechanical stimuli of osmotic stress, cell indentation, membrane suction, and ultrasound to discover mechanically sensitive ion channels involved in the bilayer model, including Piezo proteins, transient receptor potential (TRP) channels, two-pore potassium channels (K2P), transmembrane protein 16/Ancatamin (TMEM16/Ano).[39,40] However, these approaches failed to activate ASICs, which are gated via tether-mode mechanotransduction.[41–43] To determine what mechanically sensitive ion channels are involved in tether-mode mechanotransduction, we developed a substrate deformation-driven neurite stretch (SDNS) approach with neurite-bearing neurons cultured on ECM (e.g., fibronectin or laminin)-coated elastic substrate (e.g., polydimethylsiloxane) and single neurites stretched via substrate deformation (Fig. 1a).[44] By using the SDNS approaches, we found that ASIC3 is a dual function protein involved in both acid-sensation and mechano-sensing of the tether model in dorsal root ganglia proprioceptors.[45] Furthermore, we

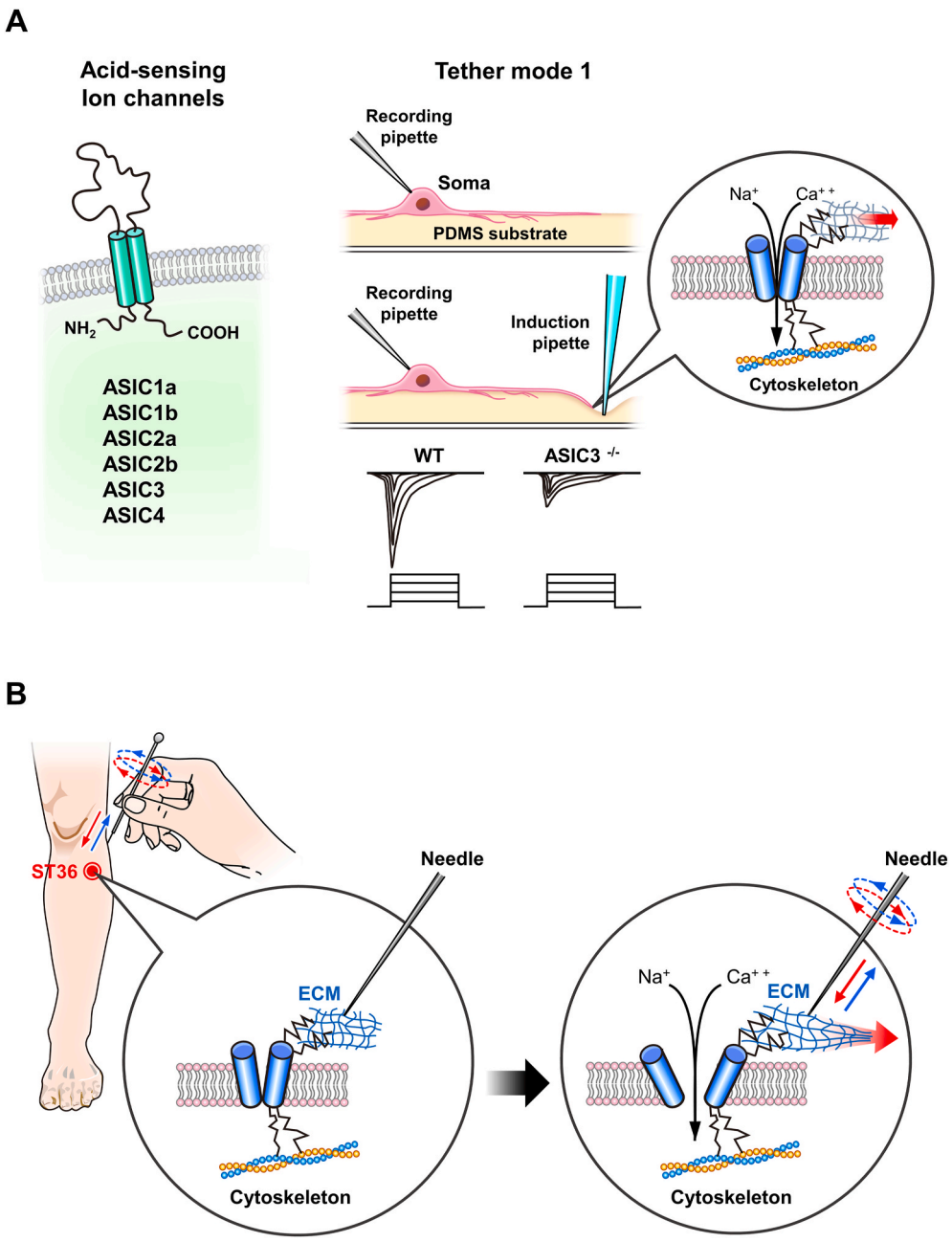

Fig. 1. A hypothetical model of manual needling-driven sngception. (A) Acid-sensing ion channels (ASICs) are two-transmembrane proteins widely expressed in somatosensory neurons. There are at least 6 ASIC subtypes (ASIC1a, ASIC1b, ASIC2a, ASIC3, and ASIC4), which can assemble as homotrimeric or heterotrimeric channels in responding to tissue acidosis and a tethering force. In an in vitro system, tether-mode mechanotransduction can be examined via a substrate deformation-driven neurite stretch (SDNS) approach, by which neurite-bearing sensory neurons are cultured on an extracellular matrix (ECM) protein-coated elastic substrate (e.g., polydimethylsiloxane [PDMS]) and stretched via a pipette indentation on the elastic substrate. Whole-cell patch clamp recordings can reveal an ASIC-dependent SDNS-induced inward current. (B) In acupoints (e.g., ST36), an acupuncture needle can easily stick to extracellular matrix (ECM) proteins (e.g., fibronectin and laminin). While the acupuncture needle is manually lifted, thrusted, and twisted, it will mingle with ECM and deliver a pulling force to ECM-tethered mechanically sensitive ion channels (e.g., acid-sensing ion channels) on somatosensory nerves to induce sngception.

recently developed a micropipette-guided ultrasound approach to selectively activate ASIC1a via tether-mode mechanotransduction.[46] Of note, the required ultrasound energy levels to activate ASIC1a are 10–100 lower than those needed for activating TRP channels or other mechanically activated ion channels gated via a bilayer model.[47]

From a molecular aspect, mechanically sensitive ion channels of the tether model such as ASICs are possible candidates to convert the mechanical force of needle lifting, thrusting, and twisting to electrical signaling in acid-sensitive somatosensory nerves because needle insertion and movement would hardly contact the nerve terminals to alter the neuronal membrane tension during acupuncture. In contrast, an acupuncture needle can easily stick to ECM proteins (e.g., fibronectin and laminin), which are widely distributed in connective tissues. Therefore, needle lifting, thrusting, and twisting can mingle with ECM proteins and deliver a pulling force to ECM-tethered ion channels on nerve terminals (Fig. 1b). Hypothetically, manual needling would be effective to activate ASICs and trigger sngception because ASICs are gated via tethering elements and enriched in somatosensory nerves. Also, activation of ASICs can trigger the release of substance P from muscle afferents to mediate antinociceptive signaling

peripherally.[29,37,48,49] Of note, the *de qi* of manual acupuncture-driven sngception can explain the local analgesic effect but not remote pain relief. Also, it cannot be explained for an electroacupuncture-induced analgesic effect or other acupuncture-mediated therapeutic effects.

Although we selected ST36 as an example to portray the manual needling-driven sngception, acupuncture-induced sng (or soreness) responses are also observed in other acupoints such as LI4 and Sp6.[24,25] However, here we do not specify acupuncture manipulation techniques, such as tonification, sedation, needling frequency, and depth.[23] Further research is needed to determine whether the needling-driven sngception is specific to certain acupoints and/or requires specific manipulation techniques, because different acupoints may have distinct somatosensory characteristics of *de qi*.[50,51]

A relevant issue is to know what somatosensory neurons transmit sngception. A previous study identified specific pain descriptors that can distinguish neuronal activation via A delta fibers (pricking) and C fibers (dull or pressing).[52] However, soreness (the acid-like perception close to sng) has no discriminate function perhaps because proton-sensing ion channels/receptors are ubiquitous in all somatosensory subtypes, including A- and C-fiber nociceptors and non-nociceptors such as proprioceptors.[29] Further studies are needed to explore the neurobiology of sng sensation and perception.

6. Conclusion

Sng is a unique phenotype and can also be a powerful biomarker for *de qi* associated with successful manual acupuncture. Sngception, a specific somatosensory function of acid-sensation or tether-mode mechano-sensation, may be the ideal molecular and physiological link between sng perception and needling. The concept of sng and sngception can serve as an emerging field for research into the peripheral mechanisms of acupuncture.

Credit authorship contribution statement

Wei-Zen Sun, Chih-Cheng Chen, Jaung-Geng Lin, conceptualization; Wei-Zen Sun, Chih-Cheng Chen, writing; Jaung-Geng Lin, supervision, review, and editing.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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