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Letter

Effect of viscoelasticity on skin pain sensation

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ABSTRACT

Pain sensation may appear under long-lasting mechanical stimulation. Although people have the experience that pain sensation generally decreases with time while the stimulation remains, the underlying mechanism remains elusive. We experimentally studied the thermal and strain rate-dependent viscoelastic behavior of skin in uniaxial stretch and numerically investigated the effects of temperature and strain rate on pain sensation. The results indicate that the viscosity of skin tissue decreases with increasing temperature and reducing strain rate, which subsequently decreases the discharge frequency of skin nociceptor and thus relieves the pain sensation. The results would contribute to the understanding of pain relief mechanism and optimizing for mechanical treatment.

Skin plays very important roles in the body, including sensory, thermoregulatory and host defense, etc. [1]. Uncomfortable feeling or pain sensation may appear when skin is under extreme mechanical and thermal stimulations, where the stimulation may be long-lasting (even hours) in some cases. For instance, in traditional Chinese cupping treatment [2] and furuncle disease [3], we feel pain due to continuous mechanical stimulation in skin tissue. Although people have the experience that uncomfortable feeling or pain sensation generally decreases with time even if the stimulation remains, the underlying mechanism is still elusive. However, it is well-known that skin is a viscoelastic material, therefore we hypothesize that its viscoelastic property may play an important role in pain sensation.

Traditionally, pain can be classified as neuropathic pain, inflammatory pain and nociceptive pain, where the physiology of nociceptive pain has been studied extensively [4]. In nociceptive pain, nociceptors transduce a noxious stimulus into ionic current that generates action potentials (discharge). The discharge is subsequently transmitted via nerve fibers from the peripheral sensory site to the synapse in the central nervous system, where the action potentials are converted into neurotransmitter release at the presynaptic terminal [5]. Neuroscientists believe discharge frequency is the main factor in the encoding of pain [6], as reflected by the increased pain intensity with increasing discharge frequency in intimated experiment [7,8]. Although several mathematical models have been used to study the thermal and mechanical skin sensation [1,9], the effect of skin viscoelasticity on nociceptive pain sensation has not been explored yet.

In this paper, we first characterized the viscoelasticity of pig dorsal skin via a uniaxial tensile experiment under different temperatures and strain rates, and analyzed the viscoelastic properties of skin by using the quasi-linear viscoelasticity (QLV) model (Fig. 1). Then, combining the QLV model and our previous pain sensation model of skin nociception, we compared the frequency of action potential induced by mechanical stimulation with and without considering skin viscoelastic properties and analyzed the effect of viscoelasticity on skin pain sensation.

The specimen is from the belly of adult pig with dimensions 12 mm × 12 mm × 2 mm. The viscoelastic behaviors of skin were studied using a computer-controlled uniaxial tensile equipment, where details concerning the experiment equipment and materials preparation can be found from our previous study [10]. In brief, the pig dorsal skin was placed at the central of a chamber filled with buffer solution. The thermal environment was controlled by

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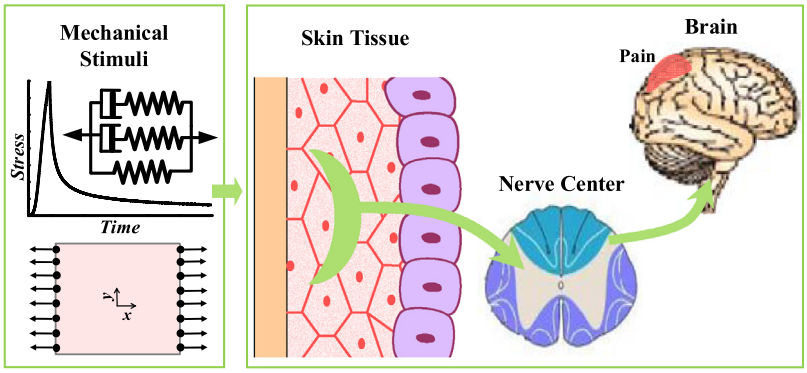

Fig. 1. A model of pain sensation in viscoelastic skin.

a circulation system connected to a thermostat. Before starting, preconditioning process was performed at 37°C to ensure a reproducible response. Both ends along the fiber direction were evenly fixed by 18 hooks (Fig. 1), a square of nine dots were marked on the skin sample to record strain in each direction using a video camera, and in-plane loads were measured by temperature compensated force transducers. The fiber direction was loaded under a range of environment temperature T (25°C, 37°C, 50°C, and 60°C) as well as loading rate γ (5%/min, 10%/min, 25%/min, and 50%/min), which is equal to strain rate.

The QLV model was used to describe the viscoelasticity of skin tissue, which can be obtained as:

$$\sigma(t) = \int_0^t g(t-\tau)\frac{\partial \varepsilon}{\partial \tau}\frac{\partial \sigma^e(\varepsilon)}{\partial \varepsilon}\mathrm{d}\tau, \tag{1}$$

where σ^e is the transient stress and g is the relaxation function, which can be approximately described by using the prony series as:

$$g(t) = k_0 + k_1 \mathrm{e}^{-t/\tau_1} + k_2 \mathrm{e}^{-t/\tau_2}. \tag{2}$$

Here, the percentage of stress at the equilibrium state of relaxation process $k_0 + k_1 + k_2 = 1$, and τ_1 is the long- and short-term relaxation time. The instantaneous response is described by the following expression:

$$\sigma^e = A\left(\mathrm{e}^{B\varepsilon} - 1\right). \tag{3}$$

The strain is given by loading rate, as:

$$\varepsilon(t) = \begin{cases} \gamma(t - t_0), & 0 \le t \le t_R \\ \gamma(t_R - t_0) = \varepsilon_{\max}, & t_R \le t \le t_\infty. \end{cases} \tag{4}$$

The stress can be expressed by substituting Eqs. (2)–(4) into Eq. (1), as:

$$\sigma(t,\theta) = \begin{cases} Ak_0\left(\mathrm{e}^{B\gamma t} - 1\right) + \sum_{i=1}^{2} \dfrac{AB\gamma k_i}{B\gamma + (1/\tau_i)} \\ \quad \times \left(\mathrm{e}^{B\gamma t} - \mathrm{e}^{-t/\tau_i}\right), \quad 0 \le t \le t_R \\ Ak_0\left(\mathrm{e}^{B\gamma t_R} - 1\right) + \sum_{i=1}^{2} \dfrac{AB\gamma k_i}{B\gamma + (1/\tau_i)} \\ \quad \times \left(\mathrm{e}^{(t_R - t)/\tau_i + B\gamma t_R} - \mathrm{e}^{-t/\tau_i}\right), \quad t_R \le t \le t_\infty, \end{cases} \tag{5}$$

where $\theta = \theta(A, B, k_0, k_1, k_2, \tau_1, \tau_2)$ is a dummy function.

The signal of pain sensation starts from the opening of ion channels in nociceptors as induced by noxious stimuli. Mechanical stimulus-induced current (I_{st}) may be calculated as [11]:

$$I_{\mathrm{st}} = I_{\mathrm{mech}} = \frac{C_{\mathrm{mech}}(\sigma - \sigma_t)}{\sigma_t} \times H(\sigma - \sigma_t), \tag{6}$$

where σ and σ_t are the stress and mechanical pain threshold at the location of nociceptor, C_{mech} is the stress conversion constant ($\mu\mathrm{A/cm}^2$), and $H(x)$ is the Heaviside function.

The action potential model in skin nociceptors can be described as [12]:

$$\frac{\mathrm{d}V_{\mathrm{m}}}{\mathrm{d}t} = \frac{I_{\mathrm{Na}} + I_{\mathrm{K}} + I_{\mathrm{K2}} + I_{\mathrm{Leak}} + I_{\mathrm{st}}}{C_{\mathrm{m}}}, \tag{7}$$

where V_{m} is membrane potential (mV); $\mathrm{C_m}$ is membrane capacity ($\mu\mathrm{F/cm}^2$); I_{Na}, I_{K}, I_{K2} and I_{leak} are sodium, potassium, the second potassium and leakage current components ($\mu\mathrm{A/cm}^2$); I_{st} is stimuli-induced current.

The discharge frequency (f) can be calculated using the following equation [1]:

$$f(V_{\mathrm{m}}) = \left[-K(V_{\mathrm{m}} - V_{\mathrm{thr}})/V_{\mathrm{m0}}\right] H(V_{\mathrm{m}} - V_{\mathrm{thr}}) \tag{8}$$

where K is a constant; V_{thr} is the firing threshold potential; C_{mech}, σ_t and V_{thr} are assumed to be 20 $\mu\mathrm{A/cm}^2$, 0.2 MPa and −55 mV [11]. The details of relevant material parameters can be found in our previous studies [12].

The mechanical properties of skin tissue are sensitive to temperature and strain rate during tensile testing [13], which may cause different pain sensation. To characterize the temperature-dependent viscoelastic behavior of skin tissue, we performed uniaxial tensile and relaxation test under different temperatures (25°C, 37°C, 50°C, and 60°C) and fixed strain rate of $\gamma = 10\%/\mathrm{min}$ (Fig. 2(a)). The stress reaches the peak value when the strain is 40%, then the stress relaxes with time. As a control, stress relaxation will not occur if viscoelasticity of skin tissue is ignored (Fig. 2(a)). We observed that the stress relaxes faster with increasing temperature when temperature is less than 50°C. The stress relaxation had no obvious change around 50–60°C. The final stress level after relaxation is much higher under low temperature than that under high temperature. The possible mechanism is that collagenous fibers, which provide the principal structural and mechanical support for skin tissue [14], were thermally desaturated under hyperthermal temperatures [15], resulting in the decrease of skin mechanical properties. With the similar method, we obtained the tensile and relaxed stress with different strain rates (5%/min, 10%/min, 25%/min, 50%/min) under a constant temperature of 30°C (Fig. 2(b)). The higher strain rate induces a higher stress peak value under the same maximal strain 40%, which exhibits the strain rate hardening behavior of skin tissue. However, we did not observe significant effect of strain rate on the final stress after stress relaxation for the same maximal strain of 40%. To quantify the effect of temperature and strain rate on the viscosity of skin tissue, we used the QLV model to fit the experimental data by using the Levenberg–Marquardt algorithms in Origin 9.0. The values of goodness-of-fit χ^2 were adopted to assess the theoretical results (Table 1), which were over 0.96. The results show that the