# Acupuncture, Connective Tissue, and Peripheral Sensory Modulation

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**ABSTRACT**: Although considerable controversy surrounds the legitimacy of acupuncture as a treatment, a growing literature on the physiological effects of acupuncture needling in animals and humans is providing new insights into basic cellular mechanisms including connective tissue mechanotransduction and purinergic signaling. This review summarizes these findings and proposes a model combining connective tissue plasticity and peripheral sensory modulation in response to the sustained stretching of tissue that results from acupuncture needle manipulation.

**KEY WORDS:** acupuncture, connective tissue, purinergic signaling, ATP, adenosine, fibroblasts, mechanotransduction

## I. INTRODUCTION

Acupuncture is an ancient healing practice that receives considerable attention for a number of seemingly paradoxical reasons. Although a recent meta-analysis has shown initial convincing evidence of its efficacy,[1] individual clinical trials of acupuncture until then had failed to demonstrate consistent superiority of acupuncture compared with sham controls, prompting many to deride acupuncture as nothing more than an elaborate placebo.[2] Meanwhile, basic research on the physiological effects of acupuncture in humans and animals has provided a plethora of findings that are of general scientific interest from the point of view of cell, tissue, and systems biology.[3] Whether these findings will eventually translate into an overall understanding of acupuncture as a treatment remains an open question. In the meantime, using acupuncture needles as tools to mechanically stimulate tissues has proven to be a fruitful approach to understand basic physiological mechanisms. This article reviews recent evidence linking connective tissue mechanotransduction and purinergic sensory afferent signaling. These mechanisms may be relevant not just to acupuncture but also to a general understanding of both connective tissue physiology and peripheral sensory modulation.

## II. EFFECTS OF ACUPUNCTURE ON CONNECTIVE TISSUE

Acupuncture needles are interesting devices for a number of reasons. First, they are extremely fine (equivalent to a 36-gauge hypodermic needle) and solid, without a cutting beveled edge, which allows them to penetrate tissue with minimal trauma. Second, their small diameter allows "loose" areolar connective tissue to wrap easily around an inserted and manually manipulated needle.[4–6] Once the needle has rotated by as little as 180 degrees, the connective tissue that has been dragged around the needle sticks to itself. This establishes a mechanical bond between needle and tissue, and the resulting "needle grasp" strengthens as the needle is manipulated further. Rotating the needle back and forth produces an immediate short-term analgesic effect in humans and animals.[7,8] How long one must manipulate the needle to elicit an analgesic effect has not been studied systematically, but most published studies have used durations of 5 minutes or more. Collagenase injected into the tissues surrounding the needle lessens these immediate analgesic effects in rats, supporting the importance of the needle–tissue mechanical bond.[9]

## III. LINK TO SENSORY MODULATION

Until recently it was assumed that the mechanisms underlying the immediate analgesic effects of acupuncture needle manipulation were centrally mediated and linked to the activation of segmental and descending pain inhibitory pathways in the brainstem and spinal cord.[10] These central "counterirritation" mechanisms are not specific to acupuncture and are shared by other types of strong prolonged stimuli (e.g., electrical, thermal). Furthermore, this type of analgesia does not require the stimulation of "acupuncture points" but can be elicited wherever the needle is placed, as long as the stimulus is of sufficient intensity and duration.

There is, in addition, recent evidence that acupuncture needle manipulation directly activates analgesic mechanisms in peripheral tissues. Takano et al.[11] and Goldman et al.[12] showed that manually rotating an inserted acupuncture needle resulted in a sustained release of adenosine triphosphate, adenosine diphosphate, and adenosine in local subcutaneous tissues that can be measured with microdialysis in mice and humans. Injection of a selective adenosine A1 receptor agonist in mice produced a transient antinociceptive effect similar to that of acupuncture. Furthermore, analgesic effects produced by either the agonist or acupuncture needle manipulation did not occur in knockout mice lacking the adenosine A1 receptor. Interestingly, this peripheral analgesic effect of acupuncture in mice was observed in the foot in response to acupuncture administered at the knee. One possible explanation for these findings is that the adenosine released acted on sensory nerves originating in the foot and passing through the tissues surrounding the knee near the location of the acupuncture needle. An alternative explanation is that acupuncture needle manipulation at the knee caused the release of adenosine not only in the local connective tissues but also along the connective tissue planes connecting the knee to the foot. This hypothesis is supported by recent evidence that acupuncture needle manipulation in mice causes measurable cellular responses in connective tissue fibroblasts several centimeters away from the needle.[13] When acupuncture needles are rotated, winding and pulling collagen around the needle creates a "whorl" around the needle that persists for 15–20 minutes when the needle is left in place, which results in sustained "internal" stretching of connective tissue. In response to this sustained mechanical stimulus, fibroblasts expand and remodel their cytoskeleton, similar to when the whole tissue is stretched uniaxially. Importantly, stretch-induced remodeling of fibroblasts involves purinergic signaling,[14] with Rho-dependent extracellular release of adenosine triphosphate. Fibroblast-mediated responses to acupuncture, therefore, could be responsible for releasing adenosine along a plane of connective tissue some distance away from the needle, which, in mice, could extend from the knee to the foot. It is not known whether similar mechanisms could occur in humans, where distances at the macroscopic scale are obviously much greater. The location of many acupuncture "meridians" described in traditional acupuncture texts follows longitudinal connective tissue planes separating muscles.[4] Dynamic ultrasound studies during acupuncture needle manipulation in humans demonstrate that measurable deformation of connective tissue occurs at least 10 cm away from the needle, and may extend farther along intermuscular connective tissue planes, compared with connective tissue over the belly of a muscle.[15]

A perplexing claim of acupuncture is that it has lasting beneficial effects beyond temporary analgesia. An interesting possibility is that, in addition to sensory modulation, acupuncture needle manipulation could cause long-term changes in connective tissue itself. Although our understanding of connective tissue physiology lags far behind that of other musculoskeletal tissues, there is a recent resurgence of interest in the role of connective tissue in both chronic pain and the mechanism of nonpharmacological treatments including acupuncture and manual and movement-based therapies. Recent studies show that human subjects with chronic low-back pain have increased thickness and decreased mobility of connective tissue in the back. This suggests that chronic inflammation and fibrosis of connective tissue may play a role in chronic musculoskeletal pain.[16,17] *In vivo* and ex vivo experiments demonstrated that gentle, static stretching of connective tissue for 10 minutes has antifibrotic effects that are different from and, in some instances, opposite of those of longer-duration static or repetitive stretching.[18] Further studies are needed to determine whether similar antifibrotic responses can be obtained with acupuncture and, if so, the optimal needling manipulation parameters (e.g., amplitude, frequency, duration) to maximize these effects.

Figure 1 illustrates a hypothetical model based on combined connective tissue mechanotransduction and purinergic signaling. In this model, dynamic fibroblast responses to mechanical stimuli participate in the physiological response to both stretching and acupuncture. Loose connective tis-

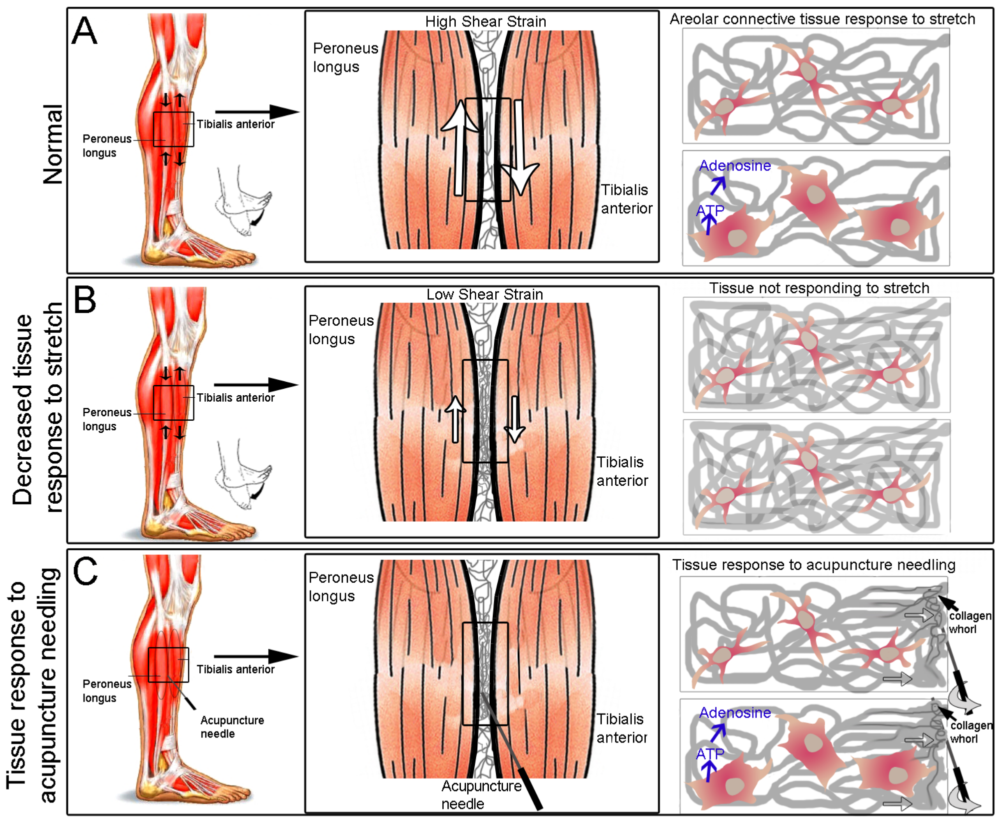


**FIG. 1:** Hypothetical model linking fibroblast responses to stretching and acupuncture.**A:** In normal connective tissue, changing the position of the foot from extended to flexed causes shear strain within "loose" areolar connective tissue separating layers of dense perimuscular connective tissue in adjacent muscles. If the foot is flexed slightly beyond the usual range of motion, and this position is held for several minutes, fibroblasts expand, remodel their cytoskeleton, and release adenosine into the tissue. ATP, adenosine triphosphate. **B:** In a local area of fibrosis and reduced shear (e.g., due to injury or inflammation), fibroblasts do not expand in response to sustained tissue stretch. This lack of cellular response over time contributes to the increasing stiffness of the tissue. **C:** Acupuncture needle manipulation performed near a fibrosed area restores the fibroblast response and adenosine release. In this model, winding and pulling collagen fibers with internal stretching of the tissue using a needle acts as a substitute for "natural" stretching.

sue is responsible for the shear plane motion (shear strain) that normally occurs between 2 adjacent muscles (Fig. 1A). Fibrosis of connective tissue due to injury or chronic inflammation causes restricted mobility, decreased shear strain, and decreased stretching of loose connective tissue during body movements. In the presence of fibrosis, a lack of fibroblast remodeling in response to tissue stretch could further stiffen the tissue and contributes to the spread of the pathology to adjacent areas[19,20] (Fig. 1B). Under such a scenario, an acupuncture needle inserted at the periphery of a fibrotic area could provide beneficial, targeted stretching of connective tissue. This would not only cause local adenosine-mediated analgesia but also encourage fibroblasts to expand, actively relax the tissue, and increase shear plane motion (Fig. 1C).

None of the connective tissue-related mechanisms discussed above seem to require that the needle be inserted at specific "acupuncture point" locations; rather, they could occur anywhere as long as the needle is inserted into connective tissue. However, acupuncture points tend to be located along intermuscular connective tissue planes and exhibit a slightly more pronounced "needle grasp" after needle rotation, most likely because the needle can be inserted into slightly deeper connective tissue at such locations.[5] It is therefore possible that fibroblast responses to acupuncture needling could be slightly enhanced at acupuncture points, although this has not been tested experimentally.

## IV. CONCLUSION

The emerging new model presented in this article proposes that mechanical stimulation of connective tissue during acupuncture needling has direct effects on restoring connective tissue health in addition to analgesic effects. These 2 types of effects could be synergistic, with initial analgesic effects providing short-term pain relief while deeper, long-term healing of connective tissue is taking place. The 2 effects together would encourage patients to move more and increase their range of motion.[21] This would provide further stretching of the tissue in a feed-forward loop between tissue remodeling, nervous system plasticity, and behavior.

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