Acupuncture mechanisms in tissue healing: contribution of NO and CGRP

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In three recent articles published in *Acupuncture in Medicine*, the possible role of acupuncture in tissue healing has been highlighted. In an article on the hypothetical action of acupuncture in the treatment of tendinopathy in the December 2012 issue of the journal, Neal and Longbottom assert that tendinopathy and tendalgia are debilitating conditions for which a gold standard treatment strategy does not exist. This is probably due to the fact that the pathophysiology of tendalgia is not well understood. However, Neal and Longbottom suggest that there is evidence—small in amount but high in quality—supporting the theory that acupuncture may be able to influence tendon healing by increasing blood flow via local vasodilation and increasing collagen proliferation, and that these effects are most likely the result of an increased release of the neuropeptide calcitonin gene-related peptide (CGRP) from sensory nerve endings. Two pathways for the vasodilation of CGRP have been described:

1. Nitric oxide (NO)-endothelium-independent pathways in which the binding of CGRP to the CGRP1 receptor on vascular smooth muscle cells induces an increase in intracellular cAMP and protein kinase A. This cascade results in opening of potassium ion channels and calcium ion sequestration followed by relaxation of vascular smooth muscle (vasodilation).

2. NO-endothelium-dependent pathways in which the binding of CGRP to the CGRP1 receptor on vascular endothelium cells triggers NO production via NO synthase. NO released from vascular endothelium leads to relaxation of vascular smooth muscle.

Neal and Longbottom also suggest that the vasodilation could be mediated by an increase in mechanical signalling through the extracellular matrix.

A possible role for CGRP in the vasodilatory response is also partly supported by Shinbara and colleagues who investigated the participation of CGRP in increasing local muscle blood flow (via the axon reflex) following manual acupuncture in rats. They reported that acupuncture treatment increased muscle blood flow without changing arterial blood pressure in intact rats. This effect was not seen in capsaicin-treated rats. On the other hand, treatment with a CGRP1 receptor antagonist reduced (but did not block) the vasodilatory effects. This led Shinbara and colleagues to suggest that other mechanisms are also involved in the vasodilatory response including adenosine phosphate compounds. These compounds may have a potent vasodilatory effect by binding to adenosine (A1 receptors) and purine receptors (P2Y receptors). Interestingly, binding adenosine phosphate compounds to their receptors on vascular endothelium cells induces NO production. Shinbara and colleagues therefore suggested that NO probably participates in vasodilation induced by acupuncture.

Zhang and collaborators recently presented an hypothesis on the role of acupuncture in tissue healing. They reported how trials have demonstrated that the acupuncture-induced axon reflex is apparent in acupuncture points in humans, particularly in the back and the abdominal region. They also suggested that the vasodilatory response observed during acupuncture stimulation could partly be attributed to the sympathetic nervous system. This suggestion is supported by studies showing dense sympathetic nerve innervation of arterioles, lymphatic vessels and mast cells. Interestingly, activity in sympathetic efferents (as during acupuncture) also mediated the release of NO.

NO, supporting the suggestions that both CGRP and NO have important roles in the vasodilatory response.

Other evidence supporting a role for NO in the vasodilatory response following acupuncture is found in the study by Kimura et al.\textsuperscript{4} They were able to reduce the vasodilatory response by administering the NO synthase inhibitor N-nitro-L-arginine methyl ester hydrochloride (L-NAME) and also raised the question of how acupuncture enhanced NO generation. They suggested that a possible explanation is that acupuncture triggers a sequential reaction, beginning with a change in sympathetic activity and leading to NO production. Another explanation could be that NO production may be caused by mechanical stimulation of the vascular endothelium (shear stress imposed on the vascular wall) during acupuncture.

Taken together, the above results suggest that acupuncture may have an important role in the periphery inducing vasodilation. The relevance of this mechanism needs to be elucidated in pathophysiological models and in clinical conditions. NO is possibly the most important factor in the short term (reversing ischaemia), whereas CGRP may be more important in the longer term as it has trophic effects on the endothelium, thereby promoting healing.

However, the most important aspect is to demonstrate clinically relevant effects in different conditions, as has recently been attempted by Zhang and collaborators in Shanghai.\textsuperscript{5} They carried out a randomised controlled trial in patients with chronic Achilles tendinopathy. The patients were randomly allocated into an acupuncture treatment group and an eccentric exercises group. The validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire was completed at baseline and at 8, 16 and 24 weeks. Pain at rest and after activity was also assessed at baseline and at 8 weeks with a visual analogue scale. The mean VISA-A score improved significantly after 8 weeks in the acupuncture group to 67.1 points and in the exercise group to 48.5 points. Acupuncture treatment resulted in a significant increase from baseline in the VISA-A score of 25.8 points after 16 weeks and 28.4 points after 24 weeks compared with increases of 10.0 points and 16.6 points after 16 and 24 weeks, respectively, in the exercise group. In the acupuncture group the pain scores were significantly more reduced than in the exercise group. Their results suggest that acupuncture treatment can reduce pain and improve activity in patients with chronic Achilles tendinopathy.

Further studies are needed to verify the clinical effects of Zhang and collaborators and to establish the stage or stages of the pathophysiological process in which the most beneficial effects of acupuncture may be achieved.

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**REFERENCES**

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