

# Acupuncture and Kidney Disease

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Acupuncture as a complex therapeutic system has been used to treat a variety of diseases and pathological conditions. Although the exact mechanism(s) of acupuncture remains unknown, some evidence suggests a mechanism initially involving signal transduction through connective tissue, with secondary involvement of other systems including the nervous system. Acupuncture has become increasingly popular in the Western countries as a therapy for pain and several chronic disorders difficult to manage with conventional treatments. Acupuncture and acupuncture-like somatic nerve stimulation have been used in different kidney diseases and several complications related to them. The effect of acupuncture techniques in some kidney diseases is reviewed on the basis of clinical reports as well as mechanisms that may possibly explain the beneficial effects mediated by acupressure/acupuncture. The potential effect of acupressure techniques in renal inflammation and whether these effects could be mediated through the newly identified cholinergic anti-inflammatory pathway are discussed.

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**Index Words:** Acupuncture; mechanotransduction; cholinergic pathway; kidney; inflammation

Acupuncture is based on natural-philosophical concepts of a state of equilibrium between different forces and organs and of the form in which this equilibrium can be maintained, either by stimulation or suppression of the energy factor via the insertion of needles into specific acupuncture points (acupoints) located on the meridians.<sup>1,2</sup> Meridians are a term of traditional Chinese medicine for the flow of vital energy accessed through acupoints. Although considerable research has been directed toward elucidating the mechanism underlying acupuncture, several fundamental aspects of acupuncture treatments remain unclear. However, it is apparent that reproducible neurologic and chemical changes occur in response to acupuncture and that these changes almost certainly modify the response to and/or perception of

pain and probably of other conditions such as inflammation.<sup>3-5</sup>

Recently, Borovikova et al,<sup>6</sup> Tracey et al,<sup>7,8</sup> and Wang et al<sup>9</sup> have shown that vagus nerve stimulation, acting through  $\alpha 7$  receptors, can inhibit significantly and rapidly the release of macrophage (M $\phi$ ) tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-6, and IL-18 and attenuate systemic inflammatory responses. These results could shed light on a number of unexplained phenomena induced by acupuncture/acupressure. They may provide a physiological mechanism for the anti-inflammatory effects mediated by acupuncture because it is well known that pain is frequently associated with acute and chronic inflammation. One of the mechanisms by which acupuncture analgesia functions to inhibit pain could be via its inhibition of the inflammatory response. Acupuncture has been suggested to increase parasympathetic nerve stimulation and decrease proinflammatory cytokine levels.<sup>10</sup>

In this article, we will summarize studies that may now provide scientific grounding for meridian therapy. We will describe the effect of different acupuncture techniques in the treatment of chronic kidney disease (CKD) and its complications. We will also present our more recent work regarding the effects of acupressure on crescentic glomerulonephritis. Our findings suggest that an acupressure-mediated anti-inflammatory ef-

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fect in the kidney might be vagus-nerve dependent.

## Mechanism of Action of Acupuncture

### Mechanotransduction

Acupuncture, a complex therapeutic system used in China for more than 2,000 years, has become increasingly popular nowadays in many parts of the world as a therapy for pain and a wide variety of mostly chronic disorders difficult to manage with conventional treatment.<sup>2,11</sup> According to the traditional Chinese medical theory, thin metal needles are inserted through the skin to reach structures in which energy paths are thought to connect specific acupuncture points along meridians that supposedly are related to internal organs. The aim of the treatment is to balance and normalize disturbances in energy flow associated with disease.<sup>12,13</sup> Mechanistic models of acupuncture based on laboratory experiments performed over the past years have mostly abandoned these traditional concepts in favor of studying the effects of acupuncture as taking place essentially through the nervous system. A fundamental distinction therefore currently exists between traditional and scientific views of acupuncture.

It has been suggested that the sense of needling touch and transduction of needling stimulation signals during acupuncture are mediated by activation of mechanosensitive stretch-activated ion channels.<sup>14</sup> Acupuncture meridians may be mechanosensitive pathways that are consistent with easily activated and/or high-density stretch-activated channels in biological systems. Langevin and coworkers<sup>4</sup> have found that mechanical signals created by acupuncture needle manipulation can induce intracellular cytoskeletal rearrangements in fibroblasts. Potentially powerful effects may derive from this mechanical signal transduction, including autocrine and paracrine cellular effects, with modification of the surrounding extracellular matrix. Mechanotransduction leads to autocrine release of growth factors, activation of extracellular-regulated kinase, and binding to extracellular membrane receptors. Brief mechanical stimuli in cells induce significant increases in cFos, Cx43, and tumor growth factor  $\beta$ . Increased

gene expression in response to mechanical stress has also been shown in tissue explants and in vivo.<sup>15</sup> Indeed, acupuncture induces c-Fos expression in the nucleus accumbens and striatum of the rat.<sup>16</sup> Accordingly, Langevin and coworkers<sup>17</sup> have proposed that the insertion and manipulation of acupuncture needles may have therapeutic effects based in the following mechanism: mechanical coupling of needle to connective tissue, winding of tissue around the needle, generation of mechanical signal by pulling of collagen fibers during needle manipulation, and mechanotransduction of the signal into cells.<sup>4,15,18,19</sup> Mechanical stimulation initially involving signal transduction through connective tissue, with secondary involvement of other systems including the nervous system, is closer to traditional Chinese acupuncture theory and also compatible with the previous proposed neurophysiological mechanisms. One of the most controversial issues in acupuncture research is whether the needling of acupuncture points has specific physiological and therapeutic effects compared with nonacupuncture points.

Mapping acupuncture points in serial gross anatomic sections through the human arm has shown an anatomic correspondence of acupuncture points and meridians to connective tissue planes. It is proposed that acupuncture needle manipulation produces cellular changes that propagate along connective tissue planes. These changes may occur wherever the needle is placed but may be enhanced when the needle is placed at specific acupuncture points.<sup>19</sup>

### Neurologic Mechanism

A number of observations have been made on experimental models that lend support to the idea that acupuncture is at least partially mediated through the autonomic nervous system. Acupuncture has been shown to decrease heart rate (HR) in humans via facilitation of cardiac vagal activity and suppression of cardiac sympathetic nerves because the acupuncture-induced HR response was attenuated by administration of atropine and propranolol.<sup>20</sup> Acupuncture produces an increase in cerebral blood flow in the cortex of anesthetized rats. This response was proven to be a reflex in which the efferent arc involved intracranial

cholinergic nerve fibers originating in the nucleus basalis of Meynert.<sup>21</sup> Electroacupuncture stimulation of the hindlimb of anesthetized rats increases gastric acid secretion. After vagotomy, no response to electroacupuncture stimulation was observed, whereas an enhancement response was seen after sympathectomy, suggesting that this response is mediated by vagus nerve stimulation.<sup>22</sup> In humans, electroacupuncture tends to normalize the leukocyte pattern. Subjects with low levels of granulocytes and high levels of lymphocytes and subjects with high levels of granulocytes and low levels of lymphocytes shifted their leukocyte pattern toward normal after electroacupuncture. This response was associated with a decrease in the HR, suggesting that parasympathetic nerves could modulate the leukocyte pattern.<sup>23</sup>

In the kidney, the facilitation of urine sodium excretion by electroacupuncture in response to hypertonic saline is abolished by bilateral denervation of the kidneys.<sup>24</sup> In experiments performed in conscious spontaneously hypertensive rats (SHR) and their normotensive control Wistar-Kyoto rats (WKY), electroacupuncture stimulation increased mean arterial pressure (MAP) and HR in both SHR and WKY rats. After termination of the stimulation, a progressive reduction in MAP and HR was observed. The poststimulation reduction of MAP was more pronounced and prolonged in SHR and was accompanied by a parallel decrease in splenic nerve activity. These studies imply that the poststimulation depressor response in SHR is attributable to sympathetic inhibition.<sup>24</sup>

Acupuncture has been suggested to decrease proinflammatory cytokines. In rats treated with lipopolysaccharide, acupuncture prevented elevation of body temperature and hypothalamic induction of IL-6 and IL-1 $\beta$ .<sup>10</sup> The centrally mediated effects of acupuncture have been investigated by different imaging techniques. In a study with a small group of subjects ( $n = 9$ ), lateralization of motor cortex excitability modulated by acupuncture has been shown using transcranial magnetic stimulation. Sham needle insertions did not induce significant changes of motor cortex excitability.<sup>25</sup> A pilot study of functional magnetic resonance imaging (fMRI) of the

brain during manual and electroacupuncture needle stimulation showed that electroacupuncture mainly produced fMRI signal increases, whereas manual needle manipulation produced fMRI signal decreases. It suggests that different brain mechanisms may be recruited during manual and electroacupuncture.<sup>26,27</sup>

### Neurohumoral Mechanism

Early studies from 1977 to 1980 showed that acupuncture analgesia is blocked or reversed by naloxone, an opioid antagonist.<sup>28-30</sup> The analgesic effects of electroacupuncture are mediated by opioid peptides in the periaqueductal gray matter.<sup>31</sup> Increased  $\beta$ -endorphin levels in human cerebrospinal fluid after acupuncture for recurrent pain has been reported. These data suggest that the analgesia observed in these patients may be mediated by the release of the endogenous opiate  $\beta$ -endorphin.<sup>5,32</sup> An increase in the level of cerebrospinal fluid met-enkephalin in heroin addicts treated successfully with acupuncture has been shown.<sup>32,33</sup> Acupuncture has been shown to induce a significant increase in serotonin in rat brain. Furthermore, the analgesic effect of acupuncture is significantly strengthened by the use of serotonin reuptake inhibitors.<sup>5</sup> Dopamine, through dopamine receptors, and noradrenalin, through  $\alpha$  receptors, exert antagonist effects on acupuncture analgesia. Acupuncture also decreases cerebral noradrenalin content.<sup>5,34</sup>

In SHR, serotonin precursors or serotonin reuptake inhibitors significantly enhance the acupuncture poststimulation reduction of MAP.<sup>24,35</sup> Acetylcholine has an effect on acupuncture analgesia; in rats, blockade of acetylcholine synthesis prevents the effect of acupuncture analgesia. This analgesic effect could be partially blocked by atropine and enhanced by eserine, a cholinesterase inhibitor.<sup>5</sup> The pressor effect of acupuncture stimulation in hypotensive rats has been suggested to be mediated by a cholinergic mechanism.<sup>24</sup> Recent evidence shows that nitric oxide plays an important role in mediating the cardiovascular responses to electroacupuncture stimulation through the gracile nucleus-thalamic pathway. Electroacupuncture stimulation induces neuronal

nitric oxide synthase expression in the gracile nucleus accompanied by c-Fos label in the dorsal medulla-thalamic tracts.<sup>36-38</sup> These studies support the notion that acupuncture has a fundamental effect on many central neurotransmitters, probably as a secondary result of the neural effect of acupuncture.

### Psychological Mechanism

It is not clear whether any specific psychological variables affect the outcome of acupuncture therapy. All therapies have a placebo effect, and acupuncture is no exception to this general rule. Controlled studies have shown that the placebo effect of a technique similar to that of acupuncture is equivalent to that expected from placebo medication (30%).<sup>5</sup>

## Modulation of Immune Responses by the Nervous System

### Cholinergic Anti-inflammatory Pathway

The understanding of the basic mechanisms that regulate inflammation has been advanced by the identification of a neural mechanism that inhibits macrophage ( $M\phi$ ) activation through parasympathetic outflow. A cholinergic anti-inflammatory pathway has been proposed because acetylcholine is the principle parasympathetic neurotransmitter and macrophages ( $M\phi$ ) that are exposed to acetylcholine are effectively deactivated. Acetylcholine significantly attenuates the release of cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-18 but not the anti-inflammatory cytokine IL-10.<sup>6,7</sup> Direct electrical stimulation of the peripheral vagus nerve in vivo during lethal endotoxemia in rats inhibited TNF synthesis in liver, attenuated peak serum TNF levels, and prevented the development of shock. By contrast, vagotomy significantly exacerbates TNF responses to inflammatory stimuli and sensitizes animals to the lethal effect of endotoxin.<sup>6</sup> This anti-inflammatory pathway has been shown in other models of systemic and local inflammation. The cholinergic anti-inflammatory pathway is localized, rapid, and discrete, but it can also induce systemic humoral anti-inflammatory responses.<sup>6-8</sup>

The molecular dovetail between the cholin-

ergic nervous system and the innate immune system is the nicotinic acetylcholine receptor  $\alpha 7$  subunit. Electrical stimulation of the vagus nerve inhibits TNF synthesis in wild-type mice but fails to inhibit TNF synthesis in  $\alpha 7$ -deficient mice. Thus, the nicotinic acetylcholine receptor  $\alpha 7$  subunit is essential for inhibiting cytokine synthesis by the cholinergic anti-inflammatory pathway.  $M\phi$  are significantly more sensitive to cholinergic agonists than peripheral blood mononuclear cells. The sensitivity of  $M\phi$  to acetylcholine suggests that other cells that produce acetylcholine, such as epithelial cells, T lymphocytes, and endothelial cells, might also participate in modulating the function of adjacent tissue macrophages.<sup>9,39</sup>

Knowledge of the cholinergic anti-inflammatory pathway is yielding insight into physiological pathways and therapeutic strategies. For example, CNI-493, a tetravalent guanilylhydrazide inhibits TNF synthesis and inflammatory responses in animal models of local and systemic inflammation. Recent evidence has shown that the TNF-suppressing activities of CNI-1493 in vivo are dependent on the cholinergic-anti-inflammatory pathway and that CNI-1493 functions as a pharmacological stimulator of the vagus nerve.<sup>7,40</sup>

The identification of this novel mechanism through which the nervous system can modulate macrophage function could explain the anti-inflammatory effects of Pavlovian-type conditioning, hypnosis, and meditation. Behavioral conditioning using models of learned association can influence acute inflammatory responses and alter the course of experimental inflammatory diseases in animal and humans.<sup>7,39,41</sup> Hypnosis and meditation can increase vagus nerve output and can inhibit immediate-type and delayed-type hypersensitivity responses.<sup>7,39,42</sup> It will be worth examining whether these effects, as well as reported beneficial effects of prayer and acupuncture on inflammation, which is known to depend on acetylcholine, are mediated by the vagus nerve and the  $\alpha 7$  subunit.<sup>3,7,8,39</sup>

### Acupuncture and CKD

*Acupuncture for kidney pain.* Acupuncture has been used in China and partly accepted in

western countries, mainly as a pain-relieving method. Both acute and chronic pain is a common complaint in patients with autosomal dominant polycystic kidney disease, affecting about 60% of patients. The pain may be related directly to renal cyst growth or complications caused by massive cysts. Pain related to autosomal dominant polycystic kidney disease is frequently manifested as chronic back pain. In a proposed stepwise sequence in the treatment of pain beginning with analgesics, physical measures such as acupuncture have been placed in second place and transcutaneous electrical nerve stimulation in third place. Acupuncture and electrical stimulation of acupuncture point are minimally invasive and prevent the side effects of analgesics.<sup>43-45</sup> Acupuncture has been frequently used to treat renal colic-associated pain in which viscerovisceral reflexes are involved.<sup>46-48</sup> In a prospective randomized study, acupuncture (22 patients) was compared with the effect of a conventional analgesic (16 patients). Acupuncture was as effective in relieving renal colic as the analgesic, but acupuncture had a more rapid analgesic onset ( $3.14 \pm 2.88$  minutes *v*  $15.44 \pm 7.55$  minutes).<sup>46</sup> In a study with 182 patients treated with acupuncture for renal colic, efficacy of analgesia was 100%; however, no control group was included.<sup>48</sup> Acupuncture may be helpful in the treatment of renal colic in selected cases such as positive history of analgesic allergy and no response to conventional analgesics.

**Acupuncture in hypertension.** Electroacupuncture in conscious SHR decreases blood pressure with a maximal fall in blood pressure of 20 mm Hg 1 hour after starting treatment. Significant bradycardia was also found. These effects were not observed in 1-clip, 2-kidney renal hypertensive rats, a type of secondary hypertension that lacks the central autonomic hyperreactivity.<sup>49</sup> However, systolic blood pressure and plasma renin activity reduction have been reported with acupuncture in 1-clip, 2-kidney renal hypertensive rats.<sup>50</sup> Whether acupuncture can affect plasma renin activity remains to be determined.

In 10 subjects with diastolic hypertension, a significant, immediate poststimulation reduc-

tion of diastolic blood pressure was observed in the electroacupuncture group compared with the sham group, which received electric stimulation in non-acupuncture-point areas.<sup>51</sup> Further studies are needed to determine whether the treatment effect can last for a significant period of time.

**Acupuncture in other kidney diseases and for the treatment of lower urinary tract symptoms.** In patients with kidney damage secondary to hyperuricemia, acupuncture treatment in 42 cases decreased the levels of uric acid, creatinine, and proteinuria; however, this study did not have an adequate and appropriate control group, and histological data were not presented.<sup>52</sup> In a randomized study, acupuncture reflexotherapy decreased the sensory irritative components of lower urinary tract symptoms that persist after transurethral resection of the prostate. Patients were divided into 3 groups of treatment: acupuncture reflexotherapy ( $n = 13$ ); placebo ( $n = 14$ ); or oxybutynin ( $n = 15$ ), an anticholinergic used to treat bladder overactivity. The patients were evaluated 1 year after the study started showing that daytime voiding decreased by 8% in patients who received oxybutynin and 20% in patients who underwent reflexotherapy, whereas the average number of nocturnal micturitions decreased 20% and 60% in patients who received oxybutynin and reflexotherapy, respectively. It was suggested that a direct effect on the proximal urethra by peripheral block of the irritative signals and modulation of the autonomic control of the urethra are the mechanisms by which acupuncture reflexotherapy may be beneficial during sensory urgency.<sup>53</sup>

**Acupuncture in the treatment of uremic pruritus.** The association between kidney failure and pruritus is well known. Although not a life-threatening complication of kidney failure, pruritus is one of the most vexing and disturbing symptoms. Pruritus occurs in 25% to 49% of patients with kidney failure. Pruritus is reported to affect 50% to 90% of patients undergoing peritoneal dialysis or hemodialysis.<sup>54,55</sup> The mechanism underlying uremic pruritus is unclear, and effective treatment is difficult. Suggested potential mechanisms include uremic toxins, hyperparathyroidism, histamine, allergic sensitization, proliferation

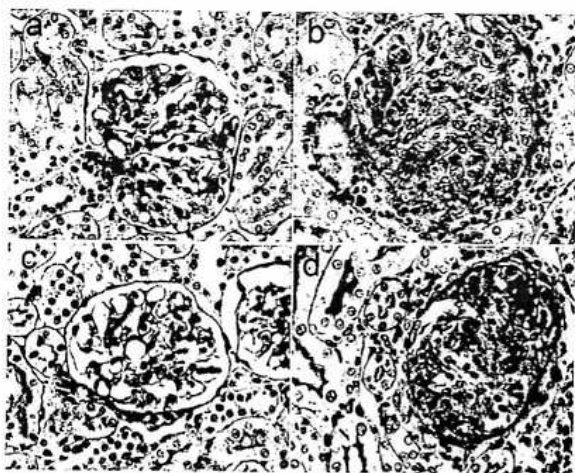
of skin mast cells, hyperavitaminosis A, iron-deficiency anemia, neuropathy, psychogenic factors, and probably a combination of these.<sup>55-57</sup> It has been suggested that the cornerstone of pruritus therapy is regular, intensive, efficient dialysis; correction of the anemia; and control of hyperphosphatemia.<sup>55,57,58</sup> Treatments include oral or topical agents, the use of non-complement-activating dialysis membranes, compliance with dietary restrictions, and ultraviolet irradiation.<sup>56,59,60</sup> Treatment results have been highly variable, and some of the clinical trials have been flawed. An association of uremic neuropathy and pruritus is common, and in uremic neuropathy, the propagation of touch and pain stimuli can be distorted, giving way to itching. Indeed, neuropathy and neurologic changes are considered a mechanism underlying uremic pruritus. Accordingly, and because acupuncture is suggested to exert its action by neurohumoral reflexes, acupressure, a technique related to acupuncture, and electrical needle therapy have been used in the treatment of uremic pruritus. In patients treated with acupressure ( $n = 30$ ) 3 times a week for a total of 15 sessions, mean pruritus scores were significantly reduced compared with the control group ( $n = 30$ ). No difference in biochemical tests was identified between both groups. Interestingly, patients treated with acupressure reported relief in joint pain, muscle cramps, sleeplessness, and some skin changes.<sup>61</sup> Electrical needle therapy, a modified acupuncture technique, has been reported also to improve uremic pruritus when compared with patients treated with superficial electrical stimulation. Electrical needle stimulation was administered for 20 minutes 3 times a week in 6 patients. In 4 patients, relief persisted for months after the end of the series of treatments. No changes in biochemical parameters were found between treated and control patients.<sup>62</sup> In this study, an increase in sleeping hours was observed in patients treated with electrical needle stimulation. Adequate dialysis, with dietary restrictions, and phosphate-binding therapy are suggested to be the most effective treatments for uremic pruritus. However, patients that do not respond to conventional treatment may benefit from acupuncture.

*Role of acupressure in improving the quality of sleep and quality of life in patients with end-stage renal disease.* Although considerable progress has been made in the treatment of CKD, sub-optimal quality of life continues to be a significant problem for these patients. Sleep disturbance is very common in patients with end-stage renal disease (ESRD). The prevalence rate of sleep alterations ranges from 50% to 80% in dialysis patients.<sup>63,64</sup> Studies in the general population have shown that poor or reduced amounts of nocturnal sleep and excessive daytime sleepiness adversely affect quality of life and functional health status. Both problems have also been associated with cardiovascular disease.<sup>65,66</sup> In patients with ESRD, poor nocturnal sleep and increased daytime sleepiness are associated with reduced quality of life.<sup>67</sup>

Over 50% of ESRD patients report symptoms of persistent fatigue that is independent of anemia. Fatigue in ESRD patients is a distressing and disabling symptom that interferes with their quality of life.<sup>68</sup> Fatigue is associated with sleep disturbance; therefore, fatigue and quality of sleep should be assessed simultaneously. Although numerous pharmacological and/or cognitive behavioral techniques are used to treat sleep disturbance, controlled clinical trials designed to evaluate their effectiveness in ESRD remain to be conducted.

Acupressure has been reported to improve the quality of sleep and fatigue in patients with ESRD. In a randomized study, the acupressure group ( $n = 35$ ) and the sham acupressure group ( $n = 32$ ) received acupoints or no acupoints massage 3 times a week for 4 weeks. In the acupressure group, a significantly decreased wake time was reported and an improved quality of sleep at night was found compared with the sham and control groups. The quality of life in acupressure group patients was improved. It has been suggested that the stimulation of acupoints may increase the release of serotonin, which induces relaxation and consequently could induce sleep.<sup>69</sup> Serotonin has been previously suggested as a neurohumoral mechanism of action of acupuncture.<sup>5</sup>

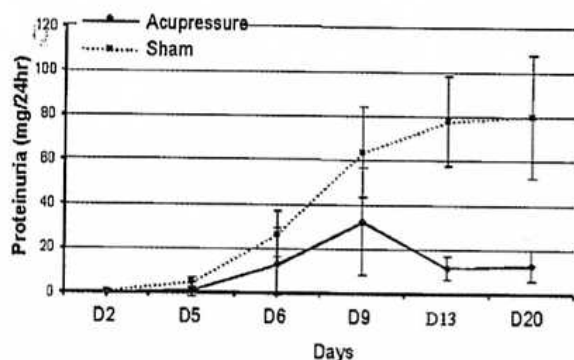
It has been reported that patients with ESRD treated with acupressure ( $n = 35$ ) expe-



**Figure 1.** Photomicrographs (original magnification,  $\times 400$ ) of the glomeruli from WKY rats with anti-GBM GN. Periodic acid-Schiff staining of rats that were treated with acupressure (A and C) or with sham pressure (B and D). Sections were sampled on day 7 (A and B) and day 13 (C and D) after anti-GBM Ab injection.

rience less fatigue and less perception of fatigue compared with the sham group ( $n = 35$ ) and control group ( $n = 36$ ). These results are probably because of acupuncture/acupressure-mediated neurohumoral mechanisms, including the endogenous opioid system, to improve mood-mediated behaviors and facilitating psychological well-being.<sup>70,71</sup>

**Does acupuncture prevent kidney inflammatory diseases?** Based on the studies mentioned previously, a mechanism initially involving signal transduction through connective tissue, with secondary involvement of other systems including the vagus nerve activity may ex-



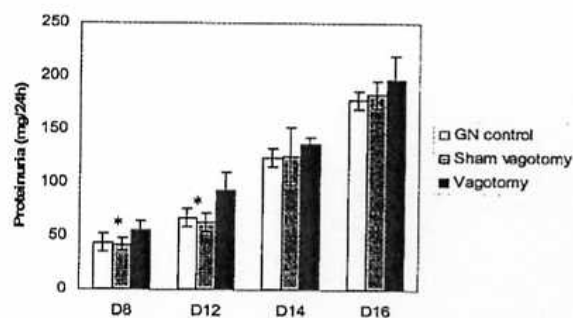
**Figure 2.** Proteinuria in WKY rats with anti-GBM GN treated with acupressure (solid line) or sham pressure (dotted line). Results were sampled from 6 rats per group and expressed as mean  $\pm$  SD. \* $P < .001$ , Student  $t$  test.

plain local and remote effects of acupuncture. It is likely that all these processes represent part of a common pathway that remains to be identified.

In view of these scientific data, we have used a model of experimental renal inflammation to investigate the potential anti-inflammatory effects of acupuncture in kidney diseases. Using an experimental model of macrophage-mediated glomerulonephritis (GN),<sup>72</sup> we have investigated the effect of acupressure in renal inflammation. Acupressure exerts effects similar to acupuncture and is noninvasive. We found that leukocyte infiltration, glomerular hypercellularity, crescent formation, and proteinuria were significantly attenuated by acupressure treatment (Figs 1 and 2).

We further investigated the potential anti-inflammatory pathway of acupressure. We hypothesized that acupressure related anti-inflammatory effects might be vagus nerve dependent. Because  $\alpha 7$ -bearing  $M\phi$  plays an important role in leukocyte infiltration and glomerular injury during antiglomerular basement membrane (GBM) GN in WKY, anti-GBM GN is an ideal model to investigate the potential cholinergic anti-inflammatory pathway of acupressure.

To determine whether acupressure-mediated anti-inflammatory effects are vagus nerve dependent, we examined how vagotomy affected renal inflammation in vivo in rats with anti-GBM GN. We found that acupressure-mediated anti-inflammatory effects were partially blocked in vagotomized rats. Reduction of proteinuria was abolished by about 50% in vagotomized rats treated with acupressure in contrast to the rats that underwent a sham surgery and were then treated



**Figure 3.** Proteinuria in WKY rats with anti-GBM GN treated with vagotomy or sham vagotomy.

with acupressure (Fig 3). These data suggest that acupressure may mediate anti-inflammatory effects through the cholinergic anti-inflammatory pathway. However, their potential use in patients with CKD and other kidney diseases remains to be determined.

### Conclusions and Perspectives

For a long time, acupuncture has been considered an empiric therapeutic skill. However, in the past decades, our current understanding of acupuncture has expanded to include not only to the level of neurons, neurotransmitters, neuromodulators, and regulatory peptides but also to the molecular biological level. Validation of effectiveness and scientific explanation of acupuncture mechanisms of action in turn will promote a justifiable popularization of acupuncture therapy.

Acupuncture has been used to treat a variety of diseases and disorders; however, in some cases, acupuncture may not be an adequate treatment. In postherpetic pain, for example, acupuncture is of little value as an analgesic therapy.<sup>73,74</sup> Our findings suggest that acupressure may be useful as a therapeutic modality for GN and provide new potential therapeutic strategies for kidney diseases. The use of CNI-1493, a pharmacological stimulator of the vagus nerve, direct stimulation of the vagus nerve or stimulation of the  $\alpha 7$  subunit could be worth developing. Moreover, we have previously shown that electric vagus nerve stimulation or pharmacological vagus nerve stimulation with CNI-1493 significantly attenuated renal inflammation during anti-GBM GN.<sup>75</sup>

On the other hand, many questions remain unclear about acupuncture, such as the specificity of the acupoints, differences among the various acupuncture techniques, and differences in the effectiveness of acupuncture among individual subject. Further studies with well-designed clinical trials will be needed to open up new prospective fields for the use of acupuncture in CKD.

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