

ACUPUNCTURE has a beneficial effect when treating many diseases and painful conditions, and therefore is thought to be useful as a complementary therapy or to replace generally accepted pharmacological intervention. The attributive effect of acupuncture has been investigated in inflammatory diseases, including asthma, rhinitis, inflammatory bowel disease, rheumatoid arthritis, epicondylitis, complex regional pain syndrome type 1 and vasculitis. Large randomised trials demonstrating the immediate and sustained effect of acupuncture are missing. Mechanisms underlying the ascribed immunosuppressive actions of acupuncture are reviewed in this communication. The acupuncture-controlled release of neuropeptides from nerve endings and subsequent vasodilative and anti-inflammatory effects through calcitonine gene-related peptide is hypothesised. The complex interactions with substance P, the analgesic contribution of β -endorphin and the balance between cell-specific pro-inflammatory and anti-inflammatory cytokines tumour necrosis factor- α and interleukin-10 are discussed.

Key words: Acupuncture, Inflammation, Neuropeptides, Cytokines, Nitric oxide

Anti-inflammatory actions of acupuncture

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Introduction

In China, acupuncture has been used in the treatment of several diseases for at least 5200 years. In Europe and the USA, this integral part of traditional Chinese medicine has become a visible component of the health delivery system and has steadily claimed its usefulness in complementary medicine. Although sometimes without a clear objective beneficial effect, an increasing number of patients, especially those suffering from chronic diseases, are seeking acupuncture treatment and pursue (lay claims to) additional healthcare. Consequently, this increases costs, even though it does not always provide a clear objective beneficial effect.¹ The widespread application of acupuncture includes the treatment of infections, inflammatory diseases like rheumatoid arthritis, autonomic dysfunction, neurological diseases like migraine, pain, cardiovascular diseases, pulmonary diseases like asthma, drug abuse, psychological disorders and many other illnesses.² Based on the effects seen in this variety of diseases, acupuncture could be divided into two main subjects: acupuncture analgesia and curative acupuncture. In general, analgesia is obtained by short-term acupuncture, whereas curative acupuncture requires long-term acupuncture treatment procedures. Traditional Chinese acupuncture is characterised by a holistic approach to the management of the disease. The skill of the acupuncturist lies in the ability to work not

only with a clear-cut diagnosis, but also takes into account the complex pattern of disease-related factors. The exact pattern and degree of disharmony is unique for each individual. Therefore, the practitioner of traditional acupuncture will approach each patient with a personalised treatment plan. This plan focuses on improving the overall well-being of the patient, rather than the isolated treatment of specific symptoms or disease.

The basic health concept in traditional Chinese medicine consists of the body's vital energy (Qi), circulating unidirectionally through a complex network of channels (meridians) just beneath the skin, but also moving within blood vessels. It permeates organs and tissues, and is behind all physiological processes. Health is the harmonious, uninterrupted flow of Qi, and disease ensues when there is disruption of Qi flow. Factors that can affect Qi flow include emotional states such as anxiety, stress, anger, fear or grief, poor nutrition, weather conditions, hereditary factors, infections and trauma. By inserting needles, the acupuncturist tries to recover the equilibrium (the equal and dynamic opposite qualities of Yin and Yang) between physical, emotional and spiritual aspects of the individual, and to improve energy flow and energy quality. Additional activation can be obtained through manipulation of the needle or electro-stimulation at different frequencies. The most common manifestations of Yin and

Yang in diseases are excess and deficiency states. Health is defined as the balance of Yin and Yang.³

Improvement of local blood circulation, distribution and bloodletting could be the main aspects of which acupuncture-derived effects in inflammatory diseases could be attributed.⁴ In the case of inflammation, differential effects of acupuncture on acute and chronic stages of the disease could be considered, more or less expressed by clinical symptoms like burning pain, redness, swelling, changing temperature and loss of function. Beyond these manifestations, inflammatory mediators could represent subsequential mechanisms that are involved, but could also represent disease activity. For example, in inflammatory bowel disease, the blood flow is increased and vascular resistance diminished,⁵ whereas the release of different inflammatory mediators is time and region dependent and could be influenced by external factors.⁶⁻⁸ In acupuncture, the insertion of a needle induces marked changes close to the needle in all the different tissues that are penetrated. These peripheral events might improve tissue function through vasodilatation in the skin due to axon reflexes, which cause an immediate flare reaction.⁹ This vasodilative effect could be caused by the release of calcitonin gene-related peptide (CGRP) upon stimulation of A δ or C fibres.^{10,11} The local release of β -endorphin could be responsible for the short-term analgesic effect, whereas the neuropeptide-induced release of anti-inflammatory cytokines could be derived from lymphocytes and secondary activating cells, such as macrophages. In the periphery, the real level of CGRP is of crucial importance. Usually CGRP has been shown to be pro-inflammatory, but in low doses it has a potent anti-inflammatory action.¹² In this respect the release of another neuropeptide, substance P, is not likely to attribute to this phenomenon,¹³ but could regulate CGRP release from nerve endings.¹⁴

In the present review, a hypothesis is presented concerning the anti-inflammatory action of needle acupuncture through a 'dose'-related and time-related release of CGRP and a hypothesised preferential shift to the subsequent formation of anti-inflammatory cytokines.

Inflammatory diseases

In the following, a number of inflammatory diseases will be reviewed in which acupuncture treatment was initiated as a complementary therapy or replacement for conventional pharmacological intervention. Then, the role of mediators of inflammation in acupuncture will be discussed and a proposed mechanism of action to use acupuncture will be hypothesised.

Asthma

Numerous uncontrolled trials as well as a limited number of controlled trials have been published with contradictory and conflicting results after the short-term or long-term use of acupuncture in the treatment of asthma. In most studies, a relatively small number of patients were included, whereas methodological procedures were incompletely described. Various outcome parameters such as lung function, quality-of-life questionnaires and reduction of medication were used to reflect improvement of the disease.

The use of acupuncture to suppress the daily intake of orally given corticosteroids and inhaled β_2 -adrenergic agonists was investigated.¹⁵ In an open trial, patients with bronchial asthma were treated by acupuncture. This resulted in a good therapeutic effect (96% effective rate). Patients initially were treated in 15 consecutive sessions and received 10 follow-up treatments to consolidate the curative effect as marked by a decrease of corticosteroid intake and diminished use of aerosols. The investigator concluded that at least 30 sessions in 3 months should be offered to initiate this effect, followed by 10 more sessions per year to prevent a relapse. The extensive treatment with acupuncture could explain the lack of effect seen in other studies.

In a double-blind cross-over study, the effect of 2 weeks of acupuncture treatment on patients with stable asthma was investigated.¹⁶ Although a significant improvement of the quality of life and a reduction of the usage of inhaled β_2 -adrenergic agonists was observed, the respiratory function was not affected. This is in contrast with another placebo-controlled study in which patients with moderate persistent asthma, who were only treated with inhaled β_2 -adrenergic agonists, received a treatment with acupuncture four times.¹⁷ This relatively short course of treatment did not affect daily intake of inhaled β_2 -adrenergic agonists. No changes in lung functions, bronchial hyper-reactivity or symptom scores were observed.

In a randomised, controlled study, both the additive effect of acupuncture to conventional therapy and the immune-modulating effects on patients with allergic asthma was monitored.¹⁸ All patients were treated 12 times for 30 min over a period of 4 weeks. Subjective parameters like the patients' general well-being, and more objective parameters like biochemical measurements in blood, were determined before and after completion of the acupuncture treatment. General well-being significantly improved in the acupuncture group (79%) in comparison with the control group (47%). Furthermore, lymphocyte proliferation and CD3⁺ and CD4⁺ cells increased, whereas the number of eosinophils significantly decreased in the acupuncture group.

Single application of laser acupuncture performed in a double-blind, placebo-controlled, crossover study to investigate the protective effect on cold dry air hyperventilation-induced bronchoconstriction revealed no significant protection in paediatric and adolescent patients.¹⁹ Forced expiratory volume and the expiratory flow were unaffected by single laser acupuncture.

In 1991, Kleijnen *et al.* published a systematic review of 13 controlled clinical trials pertaining to the use of acupuncture in the treatment of asthma during the period 1963–1989.²⁰ Only three studies of acceptable quality resulted in favourable effects. Recently, other systemic reviews and meta-analyses of all randomised clinical trials in the published literature comparing acupuncture at real and placebo points in asthmatic patients were performed. The period 1970–2000 was evaluated by Martin *et al.*²¹ Peak expiratory flow rate, forced expiratory volume and forced vital capacity were collected as objective outcome parameters. In this analysis, no significant overall effect of acupuncture to reduce asthma could be confirmed. After induction of bronchoconstriction, however, a significant effect was observed. The authors concluded that this meta-analysis was limited due to shortcomings of the individual trials and a not clearly described use of sham acupuncture. Others who reviewed the efficacy of acupuncture in asthma concluded that up to now evidence is lacking, also due to inadequately performed investigations.^{22,23} In conclusion, mainly based on clinical outcome parameters, there is presently not enough evidence to make specific recommendations about the value of acupuncture in the treatment of asthma (Table 1).

Rhinitis

Treatment by acupuncture is frequent among adults with asthma and rhinosinusitis, and therefore should be taken into account by health-care providers.^{1,24} In acute sinusitis, acupuncture resulted in an improvement in children with chronic and recurring frontal sinusitis.²⁵ In the treatment of seasonal allergic rhinitis, acupuncture has been proven to be effective. In a small single-blind crossover study, acupuncture (three times a week during a 4-week period) improved subjective symptom scores, although a

reduction in medication was not observed.²⁶ In allergen-provoked rhinitis acupuncture, acupuncture therapy was not effective when regarding the objective criteria, although again symptoms scores as registered in the diary of complaints revealed a reduction.²⁷ Desensitisation of allergic rhinitis using acupuncture endermic points of the head with the extract of positive allergens proved to be effective in an open study including 102 cases. After a follow-up of 2 years, a significant population (72%) showed a curative effect, mainly reflected by a reduced diameter of redness and reduced swelling of the skin.²⁸

In an open study, the positive effect of acupuncture on atrophic rhinitis was demonstrated. The improvement was documented by functional changes of the nasal mucosa (mucociliary transport, secreted volume and surface temperature).²⁹

Inflammatory bowel disease

The use of alternative medicine in bowel diseases was already investigated almost two decades ago. Significantly more patients with irritable bowel syndrome (11%) appeared to consult practitioners of alternative medicine than patients with Crohn's disease (4%).³⁰ Nowadays, traditional and complementary therapies such as acupuncture are more frequently combined in the treatment, relief and control of Crohn's disease.³¹ Until now, only limited data is available for the complementary use of acupuncture in ulcerative colitis with or without moxibustion.^{32–34} These data, however, indicate that acupuncture could attribute to recovery in patients with active inflammatory bowel disease.

Rheumatoid arthritis

In another autoimmune disease, rheumatoid arthritis, which sometimes also results in the development of Crohn's disease, successful treatment with acupuncture³⁵ and moxibustion has been reported.^{36,37} Although the results clearly showed a beneficial effect in the reduction of symptomatic pain, the small sample size is a matter of concern.

In other placebo-controlled cross-over studies, in a large number of patients with rheumatoid arthritis, acupuncture could not attribute to any improvement in general health, pain request or the examination of the number of swollen joints, nor to a diminished analgesic intake.^{38,39}

Until now, the usefulness of acupuncture as a complementary and alternative medical therapy in rheumatoid arthritis still has to be demonstrated in large randomised trials.⁴⁰

Table 1. Summarised effects of acupuncture in inflammatory diseases

	Effect	Reference
Asthma	+/-	15–20
Rhinitis	+	25–29
Ulcerative colitis	+	32–34
Rheumatoid arthritis	+/-	35–39
Epicondylitis	+	41–46
Complex regional pain syndrome	+	49–52

+, Significant effect; +/-, no clear disease-related effect.

Epicondylitis

The clinical efficacy of acupuncture was also investigated in chronic lateral epicondylitis of the elbow (tennis elbow). The immediate analgesic effect of a single acupuncture stimulation in a placebo-controlled single-blind trial has been reported.⁴¹ In a comparative study, both classical and superficial needle insertion was studied in a short-term treatment schedule stimulating five selected acupuncture points during 10 treatments in 3 weeks.⁴² Classical acupuncture was only superior to superficial needle insertion after all treatments were applied, but not at 3-month and 1-year follow-ups. Laser treatment applied to the same acupuncture points, however, did not improve subjective and objective outcome parameters significantly in comparison with a placebo.⁴³ Psychosomatic factors could attribute significantly in the positive short-term effects of pain reduction.⁴⁴ As seen in the improvement of outcome parameters including pain scores, function, disability, strength and quality of life, short-term effects are promising⁴⁵ but acupuncture failed to stabilise the disease and did not contribute to further recovery.⁴⁶

Complex regional pain syndrome type 1

Recently, we confirmed that complex regional pain syndrome type 1 (CRPS1), formerly indicated as post-traumatic sympathetic dystrophy or Sudeck's atrophy, developed in one or more extremities, and should also be considered as the result of an inflammatory reaction after neurogenic stimulation.^{47,48} Two case reports^{49,50} and two randomised trials predominantly focused on pain reduction^{51,52} have published improvements after long-term acupuncture treatment. Other symptoms of inflammatory reactions including swelling, mobility, temperature and redness were also observed. In comparison with sham-treated patients, no significant improvement of these parameters could be proven.

Vascular diseases

Inflammation of the vascular system could attribute to some of the afore-described inflammatory diseases. The promotion of blood circulation by acupuncture could positively affect the enrolment of the whole cascade of inflammatory mediators that are undoubtedly involved in the subsequent processes during chronic inflammation.^{53,54} In the context of migraine, neurogenic inflammation could also play an important role.⁵⁵ Elevated plasma levels of CGRP during headache suggest that this initial inflammatory mediator is involved. In general, acupuncture has additional value in the treatment of primary headaches.^{56,57}

Table 2. Inflammatory mediators reported in acupuncture

Neuropeptides	Substance P Neurokinin A Neuropeptide Y Vaso-active intestinal peptide Bradykinin Calcitonine gene related peptide β -Endorphin
Cytokines	IL-1 β , IL-2, IL-4, IL-6, IL-10 IFN- γ , TNF- α
Other vaso-active substances	Nitric oxide Eicosanoids Serotonin

Inflammatory mediators

In general, inflammation is associated with increasing temperature, oedema, redness, pain and loss of function. Furthermore, the direct and indirect effects of individual neuropeptides, cytokines and vasoactive mediators⁴⁷ could be considered to play an intermediate role during and after acupuncture has been assessed. Assuming local blood flow is indeed stimulated by acupuncture,^{58,59} the neurogenic formation of vasoactive mediators could regulate blood flow and blood distribution to affected organs and tissue after inflammation has been initiated. Acupuncture activates the defence systems. It influences specific and non-specific cellular influx, activation of cell proliferation and regulation of subsequently involved cells that will result in a complex mechanism of transport, further breakdown and clearance of all bioactive mediators⁶⁰ (Table 2).

Neuropeptides

Calcitonine gene-related peptide is a potent vasodilator¹⁰ that has been shown to have a physiological and pathological role in neurogenic inflammation, migraine, thermal injury, circulatory shock, pregnancy and menopause, hypertension and heart failure, and has been proven to be cardioprotective.⁶¹ Both substance P and CGRP have important roles in oedema formation and inflammation, and when transported centrally these neuropeptides can cause excitation.⁶²

In patients with CRPS1, blood samples did not show an elevation of substance P and neurokinin A, whereas neuropeptide Y, CGRP, bradykinin and vasoactive intestinal peptide (VIP) were increased four-fold.⁶³ Intraneural substance P contributes to the severity of inflammation.⁶⁴ After intra-arterial infusion in the human forearm, substance P provoked vasodilatation, flushing and plasma extravasation.⁶⁵ In musculocutaneous flaps in the rat, increased blood flow affected by acupuncture was comparable with the effects observed after injection of substance P and

CGRP.⁵⁹ In rats, acupuncture induced the release of substance P from peripheral terminals of primary sensory neurons.⁶⁶ After repeated electro-acupuncture, significantly higher concentrations of substance P and other neuropeptides such as neurokinin A and neuropeptide Y were found in the rat brain.⁶⁷ The acute release of neuropeptides can be mimicked and easily provoked after application of capsaicin, the bioactive substance of red pepper. Acupuncture could diminish capsaicin-induced oedema in the rat paw, indicating a prominent role for substance P and other neuropeptides.⁶⁸ In dogs, the concentrations of substance P were determined in the skin, muscle and subcutis of acupoints and control points, showing an increased release of substance P after acupuncture.⁶⁹ On the other hand, an observation in rabbit tooth pulp showed that, after an initial substance P release had already been evoked, electroacupuncture suppressed this release.⁷⁰ In humans, during labour, the content of substance P in serum declined after acupuncture had been applied,⁷¹ but increased in patients suffering from fibromyalgia.⁷² In both observations the analgesic effect of acupuncture was significant. In samples taken from the saliva of healthy subjects, the release of substance P was hardly affected after acupuncture, although neuropeptide Y and CGRP were markedly increased.⁷³

Needling of acupuncture points could result in activation of afferent fibres of peripheral nerves, which induces the release of endogenous opiate peptides from nerve cells. Beta-endorphins are believed to play an important intermediate role in the regulation of the analgesic effects obtained through acupuncture.^{74,75} Beta-endorphin concentrations in spinal fluid and plasma of horses, however, were not elevated after acupuncture.⁷⁶ Although prenatal acupuncture treatment in women significantly reduced the duration of labour, serum levels of β -endorphin were not influenced.⁷⁷ In another study, however, 90 patients suffering from various painful disorders were subjected to acupuncture. Plasma β -endorphin levels were increased considerably increase, resulting in an elevated immunologic response⁷⁸ reflected by lymphocyte markers CD3, CD4 and CD8.

In curative (long-term) acupuncture, interactions between β -endorphins and cytokines could therefore result in an increased formation of anti-inflammatory cytokines⁷⁹ such as interleukin (IL)-10 and/or a diminished production of pro-inflammatory cytokines, possibly being the most prominent mechanism of action underlying the attributive effect of acupuncture in chronic inflammatory diseases. Very recently, the existence of regulatory IL-10-dependent T-cell populations was documented in allergic diseases.⁸⁰

Cytokines

Recently, the effect of acupuncture on regulation of cytokine production in asthma has been published.⁸¹ Clinical signs of asthma improved markedly. In peripheral blood of asthmatic patients, the mean IL-2 and IL-6 plasma levels were decreased, whereas interferon (IFN)- γ , IL-4 and tumour necrosis factor (TNF)- α were increased. After acupuncture IFN- γ , IL-2, IL-4 and IL-6 were elevated and TNF- α was reduced. In allergic rhinitis, plasma concentrations of IL-2, IL-6 and IL-10 were determined before and after acupuncture in comparison with healthy controls.⁸² In all allergic rhinitis patients, IL-10 levels were increased prior to real acupuncture, sham acupuncture or non-treatment. In the acupuncture group IL-10 was reduced, whereas IL-2 was hardly affected and IL-6 remained unchanged after therapy. In rheumatoid arthritis, IL-2 levels were lower than in the healthy controls.^{36,37} After acupuncture, this reduced IL-2 production was elevated. In a rat model for ulcerative colitis,⁸³ acupuncture and moxibustion inhibited the expression of pro-inflammatory cytokines IL-1 β and IL-6.

In conclusion, the (im)balance between T helper 1 cell-derived and T helper 2 cell-derived pro-inflammatory and anti-inflammatory cytokines was reset by acupuncture.

Nitric oxide

As some observations highlight the stimulating effects of acupuncture to muscle afferents and blood flow through autonomic reflexes, the attributive effect of nitric oxide (NO) through local release and/or induction after electrostimulation should also be considered.⁸⁴ Significant and persistent increases in the arteriolar diameter were observed after electroacupuncture. This effect was abolished in the presence of nitro-L-arginine methyl ester (L-NAME), indirectly indicating that NO plays a key role in the primary mechanisms that are involved in microcirculation. From rat studies, it has been shown that NO levels were increased in rat striatum after cerebral artery occlusion, ischaemia and reperfusion. Electroacupuncture antagonised the ischaemia-elicited release of NO.⁸⁵ The anticonvulsant effect of electroacupuncture might be related to the decrease of the nitric oxide synthases neuronal nitric oxide synthase and inducible nitric oxide synthase.⁸⁶ From these preliminary results it is not clear whether central effects evoked by electroacupuncture are more pronounced than those observed in the circulatory system, especially when inflammation occurs and the endothelial-derived nitric oxide synthase produces sustained amounts of NO.⁸⁷ Furthermore, a disturbed microcirculation through shunting of arterioles is also evoked by serotonin, another reasonable explanation

Table 3. Variables in acupuncture

Controlled studies	Non-treated controls
	Placebo needled acupuncture
	Sham (non) invasive acupuncture
	Laser
Style	Superficial ('minimal')
	'Wrong' acupoints
	Penetrating/invasive acupuncture
	Disease-related acupuncture
Treatment schedule	Individualised acupuncture
	Chinese traditional acupuncture
	Japanese superficial acupuncture
Needle	Western-oriented acupuncture
	Single treatment
	Frequency
	Repeated treatments short term
Stimulation	Repeated treatments long term
	Follow-up treatment
	Point selection per session
	Number of acupoints used
Blinding	Number of needles inserted
	Depth of insertion, needle type
Co-interventions	Duration of needling
	Manual
	Electrical
	Patient
	Acupuncturist
	Physiotherapist
	Assessor
	Statistician
	Moxibustion
	Herbs
	Physical therapy
	Pharmaceutical intervention

why acupuncture could be (only) effective for the short-term treatment of migraine.

Discussion

Pitfalls in methodology of measuring the use of acupuncture

In general, acupuncture trials include a limited number of patients. These trials are heterogeneous regarding patients, interventions and outcome measures and (therefore) present contradictory results. Most obvious is the need for well-designed and larger clinical trials.⁸⁸ Research in the area of complementary medicine such as acupuncture should be performed and evaluated at the same high-quality standards as research in the use of conventional therapies. In some studies, acupuncture points that were used in the sham groups could be effective according to traditional Chinese medicine. Therefore, with regard to the standardised choice of acupuncture points in the set-up of repeatedly applied acupuncture in sham acupuncture controlled clinical trials, the main problem to be solved is to determine the originally individualised treatment strategy that includes this approach.

A matter of debate is the set-up of randomised trials comparing placebo, sham or non-treatment. A placebo needle has been designed, with which it

could be possible to stimulate an acupuncture procedure without penetrating the skin.⁸⁹ In this set-up, placebo-treated patients experienced less Qi pain sensation, also expressed by a diminished visual analogue scale pain. Another acceptable approach could be the inclusion of sham laser acupuncture,⁹⁰ but it is preferred that sham acupuncture is used, when not actively involved meridians are needled or superficial pricking is applied. Based on functional magnetic resonance imaging of the whole brain, it has however been demonstrated that superficial pricking revealed more signal intensity than minimal applied acupuncture.⁹¹

From a pharmacotherapeutical point of view (kinetics, dynamics and dose finding), it is difficult to make comparisons between different acupuncture techniques that are used in not well-described studies. First, from traditional Chinese medicine, acupuncture should be considered and applied as an individually based therapy. Many factors and variables will influence the outcome of the therapy, such as: which of the acupoints and how many acupoints are chosen per treatment session? what is the reproducibility of the matrix of chosen acupoints? what is the type, depth, direction and manipulation of the inserted needle? what is the needle retention time and the length of the session? what is the frequency and total number of treatments? what is the follow-up? and what are the maintenance treatments?⁹² (Table 3) Furthermore, for Western scientists, the main part of the literature describing Chinese and Japanese trials performed on acupuncture is only available as translated abstracts. Not only is there a marked difference between Chinese and Japanese acupuncture, but Western educated and qualified acupuncturists apply acupuncture differently in comparison with ancient acupuncturists. In some studies performed in Western countries, Chinese guest scientists collaborated in these studies, and they were the ones who performed the acupuncture treatments during their stay. As a consequence, some specific methodological information is missing, which makes it virtually impossible to continue or repeat treatment schedules for specific purposes (Fig. 1). Recently, standards for reporting the outcome of controlled acupuncture trials have been published.⁹³⁻⁹⁶ Because the intensity and frequency of acupuncture as a complementary therapy will be individually chosen, one should also consider the subtype of the disease. In asthma, for instance, some aspects such as allergic, acute, chronic, exercise or cold-induced asthma should be considered, which will certainly affect the outcome of the acupuncture therapy. In most studies, subjective parameters (e.g. visual analogue scale pain, life questionnaires) are used. In open and single-blinded trials, the results clearly depend on the sample size and the number of repeated measurements. Objec-



FIG. 1. A number of studies describing the application of acupuncture in inflammatory disease have been published. Conclusions are difficult to be made, due to different acupuncture techniques used and insufficiently described methodology. (Drawing by Theodoor van Baars.)

tive parameters (e.g. forced expiratory volume in one second (FEV₁), oedema or secreted volume and surface temperature) better reflect the attributive effect of acupuncture in the recovery from inflammatory diseases, but do not distinguish between primary and secondary events. Therefore, documented research on underlying mechanisms indicating the specific release or inhibitory action on the formation of inflammatory mediators such as substance P, CGRP, β -endorphin and cytokines would undoubtedly indicate whether acupuncture is advisable as a complementary therapy and confirm preliminary results.

Mechanism of action of acupuncture: a concept

The underlying mechanism of acupuncture could be that, after antidromic stimulation of the nociceptor, CGRP, substance P and β -endorphin are all released. Initially, substance P will activate mast cells and in a later phase also macrophages to secrete inflammatory mediators. As a consequence, the mast cell will not only secrete serotonin and histamine, but also cytokines such as TNF- α . In turn, TNF- α could prime sensory nerve endings.⁹⁷ The activation of mast cells and mast cell-mediated inflammation is regulated by NO.⁹⁸ Macrophages will produce a number of cytokines and eicosanoids. In the blood vessel, CGRP will directly or indirectly affect vasodilation and extravasation via the stimulation of NO,^{99,100} VIP and bradykinin. Delayed dilatation to bradykinin is cyclooxygenase-2 dependent,¹⁰¹ whereas prostaglandin E₂ potentiates bradykinin and induces pain. Substance P regulates the vasodilator activity of CGRP through the action of proteases from mast cells.¹⁴ In calcitonin/alpha calcitonin gene-related peptide knockout mice, nociceptive hypersensitivity was reduced.¹⁰² Furthermore, it has been shown that both CGRP and VIP counteract nicotine-induced sweating.¹⁰³ The suppressing or potentiating effects of substance P and CGRP on metacholine-mediated

cholinergic sweating, however, were dose dependent.^{104,105} The ability of sweating to regulate skin temperature is well known and is more pronounced in men than in women. In women with chronic pelvic pain, intravenous infusion with CGRP resulted in a significant increase of skin temperature and complaints in comparison with healthy volunteers, whereas VIP did not provoke pain nor affect temperature,¹⁰⁶ suggesting the existence of a neurovascular disorder. There has been some evidence that hot flashes observed in menopausal women are due to up-regulation of CGRP receptors following ovarian hormone deficiency.¹⁰⁷ In ovariectomised rats, the greatest vasodilation and skin temperature increase was observed after CGRP, with less effect of VIP and the smallest effect seen after substance P.¹⁰⁸ In men who showed hot flashes after castration due to prostate carcinoma, plasma CGRP levels were elevated.¹⁰⁹ These results suggest that the vasodilative and skin temperature increasing effect of CGRP could be due to a diminished amount of (female) sex steroids. This could explain the higher incidence of migraine in woman¹¹⁰ and menstrual-related migraine,^{55,111} and the prevalence of some diseases in women, such as CRPS1^{47,48} and carpal tunnel syndrome.¹¹² In addition, studies on gender differences in pressure pain threshold in healthy humans showed a significant decrease in females in comparison with males.¹¹³

In general, the acute, short-term and long-term effects of acupuncture are comparable with actions observed by the use of capsaicin. Capsaicin is the bioactive component of chili pepper. Application of capsaicin to the skin^{114–116} or mucous membranes¹¹⁷ initially results in irritation and hyperaesthesia. This momentary effect is attributed to the release of substance P from peripheral sensory C fibres. Repeated application of capsaicin would result in a depleted secretion of substance P from neurons. During inflammation these effects are more pronounced.¹¹⁸ It is conceivable that the simultaneous release of CGRP will follow the same cascade of secretion. The antinociceptive effects of a capsaicin analogue, civamide, when given orally to rats, have been described.¹¹⁹ Besides the receptor related effects of this vanilloid receptor agonist and neuronal calcium channel blocker, proposed actions could also include inhibition of the neuronal release of CGRP and substance P.¹²⁰ That could explain the acute¹²⁰ and prophylactic properties¹²¹ of this substance in the treatment of cluster headaches. In concordance with these findings, therapeutic (needle) acupuncture induces peripheral events that might improve tissue function and induce local pain relief, based on mechanisms that include axon reflexes, release of neuropeptides such as CGRP, anti-inflammatory actions of neuropeptides like substance P, and local release of β -endorphin. Furthermore, sympathetic

Conclusions

A number of observations on the anti-inflammatory actions of acupuncture have been published, representing open studies and randomised trials. Both short-term and long-term treatment schedules were performed, with varying number of acupuncture points, acupuncture frequency and additional application of electro-stimulation. The value of complementary acupuncture in the treatment of inflammatory diseases is still questioned. In asthma, the highest effective rate observed was obtained after a high number of frequently applied acupuncture sessions were performed, then reduced, and then performed at least 10 times per year to prevent relapse.¹⁵ In rhinitis, results that were mainly obtained from open trials suggest a complementary effect of acupuncture after allergen provocation. In inflammatory bowel disease and rheumatoid arthritis, the usefulness of acupuncture still has to be demonstrated in large randomised trials. In epicondylitis and CRPS1, the attributive immunosuppressive effect of acupuncture has not yet been properly investigated, although a reduction of pain has been observed. From preliminary results it is conceivable to hypothesise that CGRP has a prominent role in the acupuncture-affected regulation of acute, sub-acute and chronic inflammation, regarding the vasodilative properties of this neuropeptide. Substance P should be considered to counteract the release of CGRP from nerve endings, whereas the balance of the mast cell derived pro-inflammatory TNF- α and the T-cell-derived anti-inflammatory IL-10 could contribute to the development of the chronic stage of the inflammation. In this respect, acupuncture as a maintenance treatment could be beneficial to reduce inflammation. Evidence from large randomised trials, including follow-up measurements of mediators of inflammation, both at the site of inflammation and in the periphery, should be obtained to prove the immunologic effects of acupuncture.

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References

- Schafer T, Riehle A, Wichmann HE, Ring J. Alternative medicine in allergies — prevalence, patterns of use, and costs. *Allergy* 2002; **57**: 694–700.
- Sato A, Li P, Campbell JL (Eds). *Acupuncture: is there a physiological basis? Excerpta Medica International Congress Series 1238*. Amsterdam: Elsevier Science, 2002.
- British Acupuncture Council, London, UK, www.acupuncture.org.uk
- Kaptchuk TJ. The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? *Ann Intern Med* 2002; **136**: 817–825.
- Garrelts IM, Heiligers JP, Van Meeteren ME, et al. Intestinal blood flow in murine colitis induced with dextran sulfate sodium. *Dig Dis Sci* 2002; **47**: 2231–2236.
- Van Dijk APM, Keuskamp ZJ, Wilson JHP, Zijlstra FJ. Sequential release of cytokines, lipid mediators and nitric oxide in experimental colitis. *Mediat Inflamm* 1995; **4**: 186–190.
- Zijlstra FJ, Srivastava ED, Rhodes M, et al. Effect of nicotine on rectal mucus and mucosal eicosanoids. *Gut* 1994; **35**: 247–251.
- Zijlstra FJ. Smoking and nicotine in inflammatory bowel disease: good or bad for cytokines? *Mediat Inflamm* 1998; **7**: 153–155.
- Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 2002; **136**: 374–383.
- Brain SD, Williams TJ, Tippens JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide (CGRP) is a potent vasodilator. *Nature* 1985; **313**: 54–56.
- Brain SD, Newbold P, Kajekar R. Modulation of the release and activity of neuropeptides in the micro-circulation. *Can J Physiol Pharmacol* 1995; **73**: 995–998.
- Raud J, Lundeberg T, Brodda Jansen G, Theodorssen E, Hedqvist P. Potent anti-inflammatory action of calcitonin gene-related peptide. *Biochem Biophys Res Commun* 1991; **180**: 1419–1435.
- Franco-Cereceda A, Rudehill A, Lundberg JM. Calcitonin gene-related peptide but not substance P mimics capsaicin-induced coronary vasodilatation in the pig. *Eur J Pharmacol* 1987; **142**: 235–243.
- Brain SD, Williams TJ. Substance P regulates the vasodilator activity of calcitonin gene-related peptide. *Nature* 1988; **335**: 73–75.
- Hu J. Clinical observation on 25 cases of hormone dependent bronchial asthma treated by acupuncture. *J Trad Chin Med* 1998; **18**: 27–30.
- Biernacki W, Peake MD. Acupuncture in treatment of stable asthma. *Respir Med* 1998; **92**: 1143–1145.
- Shapira MY, Berkman N, Ben-David G, Avital A, Bardach E. Short-term acupuncture is of no benefit in patients with moderate persistent asthma. *Chest* 2002; **121**: 1396–1400.
- Joos S, Schott C, Zou H, Daniel V, Martin E. Immunomodulatory effects of acupuncture in the treatment of allergic asthma: a randomised controlled study. *J All Complement Med* 2000; **6**: 519–525.
- Gruber W, Eber E, Malle-Scheid D, Pflieger A, Weinhandl E, Dorfer L, Zach MS. Laser acupuncture in children and adolescents with exercise induced asthma. *Thorax* 2002; **57**: 222–225.
- Kleijnen J, ter Riet G, Knipschild P. Acupuncture and asthma: a review of controlled trials. *Thorax* 1991; **46**: 799–802.
- Martin J, Donaldson AN, Villaroel R, Parmar MK, Ernst E, Higginson JJ. Efficacy of acupuncture in asthma: systemic review and meta-analysis of published data from 11 randomised controlled trials. *Eur Respir J* 2002; **20**: 846–852.
- Steurer-Stey C, Russi EW, Steurer J. Complementary and alternative medicine in asthma — do they work? *Swiss Med Wkly* 2002; **132**: 338–344.
- Linde K, Jobst K, Panton J. Acupuncture for chronic asthma (Cochrane Review). In: *The Cochrane Library*, Oxford: Update Software, 2002.
- Blanc PD, Trupin L, Earnest G, Katz PP, Yelin EH, Eisner MD. Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis: data from a population-based survey. *Chest* 2001; **120**: 1461–1467.
- Pothman R, Yeh HL. The effects of treatment with antibiotics, laser and acupuncture upon chronic maxillary sinusitis in children. *Am J Chin Med* 1982; **10**: 55–58.
- Xue CC, English R, Zhang JJ, Da Costa C, Li CG. Effect of acupuncture in the treatment of seasonal allergic rhinitis: a randomized controlled clinical trial. *Am J Chin Med* 2002; **30**: 1–11.
- Wolkenstein E, Horak F. Protective effect of acupuncture on allergen provoked rhinitis. *Wien Med Wochenschr* 1998; **148**: 450–453.
- Zhou RL, Zhang JC. Desensitization treatment with positive allergens in acupoints of the head for allergic rhinitis and its mechanism. *Zhong Xi Yi Jie He Za Zhi* 1991; **11**: 721–723.
- Yang J, Zhang Q. Twenty-three cases of atrophic rhinitis treated by deep puncture at three points in the nasal region. *J Trad Chin Med* 1999; **19**: 115–117.
- Smart HL, Mayberry JF, Atkinson M. Alternative medicine consultations and remedies in patients with the irritable bowel syndrome. *Gut* 1986; **27**: 826–828.
- Ballard AE. Traditional and complementary therapies used together in the treatment, relief and control of Crohn's disease and polyarthritis. *Complement Ther Nurs Midwifery* 1996; **2**: 52–54.
- Chen Z. Treatment of ulcerative colitis with acupuncture. *J Trad Chin Med* 1995; **15**: 231–233.
- Zhang X. 23 cases of chronic non-specific ulcerative colitis treated by acupuncture and moxibustion. *J Trad Chin Med* 1998; **18**: 188–191.
- Yang C, Yan H. Observation of the efficacy of acupuncture and moxibustion in 62 cases of chronic colitis. *J Trad Chin Med* 1999; **19**: 111–114.
- Man SC, Baragar FD. Preliminary clinical study of acupuncture in rheumatoid arthritis. *J Rheumatol* 1974; **1**: 126–129.
- Xiao J, Liu X, Sun L, et al. Experimental study on the influence of acupuncture and moxibustion on interleukin-2 in patients with rheumatoid arthritis. *Zhen Ci Yan Jiu* 1992; **17**: 126–128.
- Liu X, Sun L, Xiao J, et al. Effect of acupuncture and point-injection treatment on immunologic function in rheumatoid arthritis. *J Trad Chin Med* 1993; **13**: 174–178.

38. David J, Townsend S, Sathanathan R, Kriss S, Dore CJ. The effect of acupuncture on patients with rheumatoid arthritis: a randomized, placebo-controlled cross-over study. *Rheumatology* 1999; **38**: 864–869.
39. Casimiro L, Brosseau L, Milne S, Robinson V, Wells G, Tugwell P. Acupuncture and electroacupuncture for the treatment of RA. (Cochrane Review). *The Cochrane Library*, Issue 4. Oxford: Update Software, 2002.
40. Berman BM, Swyers JP, Ezzo J. The evidence for acupuncture as a treatment for rheumatologic conditions. *Rheum Dis Clin North Am* 2000; **26**: 103–115.
41. Molsberger A, Hille E. The analgesic effect of acupuncture in chronic tennis elbow pain. *Br J Rheumatol* 1994; **33**: 1162–1165.
42. Haker E, Lundeberg T. Acupuncture treatment in epicondylalgia: a comparative study of two acupuncture techniques. *Clin J Pain* 1990; **6**: 221–226.
43. Haker E, Lundeberg T. Laser treatment applied to acupuncture points in lateral humeral epicondylalgia. A double-blind study. *Pain* 1990; **43**: 243–247.
44. Berlin J, Erdman W, David E. Psychosomatic correlations in chronic pain patients using electroacupuncture. *Am J Chin Med* 1989; **17**: 85–87.
45. Fink M, Wolkenstein E, Karst M, Gehrke A. Acupuncture in chronic epicondylitis: a randomized controlled trial. *Rheumatology* 2002; **41**: 205–209.
46. Green S, Buchbinder R, Barnsley L, Hall S, White M, Smidt N, Assendelft W. *Acupuncture for lateral elbow pain (Cochrane Review)*. In: *The Cochrane Library*, Oxford: Update Software, 2002.
47. Huygen FJPM, de Bruijn AGJ, Klein J, Zijlstra FJ. Neuroimmune alterations of the complex regional pain syndrome type 1. *Eur J Pharmacol* 2001; **429**: 101–113.
48. Huygen FJPM, de Bruijn AGJ, de Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. *Mediat Inflamm* 2002; **11**: 47–51.
49. Leo KC. Use of electrical stimulation at acupuncture points for the treatment of reflex sympathetic dystrophy in a child. *Phys Ther* 1983; **6**: 957–959.
50. Hill SD, Lin MS, Chandler PJ. Reflex sympathetic dystrophy and electroacupuncture. *J Texas Med* 1991; **87**: 76–81.
51. Chan CS, Chow SP. Electroacupuncture in the treatment of posttraumatic sympathetic dystrophy (Sudeck's atrophy). *Br J Anaesth* 1981; **53**: 899–901.
52. Korpan MI, Dezu Y, Scvneider B, Leitha T, Fialka-Moser V. Acupuncture in the treatment of posttraumatic pain syndrome. *Acta Orthopaed Belg* 1999; **65**: 197–201.
53. Cheng L, Wu K, Qie Z. Role of qi in reaching affected area using acupuncture in promoting blood circulation to remove blood stasis. *Zhong Xi Yi Jie He Za Zhi* 1990; **10**: 209–211.
54. Schoen AM. Acupuncture for musculoskeletal disorders. *Probl Vet Med* 1992; **4**: 88–97.
55. Williamson DJ, Hargreaves RJ. Neurogenic inflammation in the context of migraine. *Microsc Res Tech* 2001; **53**: 167–178.
56. Manias P, Tagaris G, Karageorgiou K. Acupuncture in headache: a critical review. *Clin J Pain* 2000; **16**: 334–339.
57. Melchart D, Linde K, Fischer P, Berman B, White A, Vickers A, Allais G. Acupuncture for idiopathic headache (Cochrane Review). In: *The Cochrane Library*, Oxford: Update Software, 2000.
58. Blom M, Lundeberg T, Dawidson I, Angmar-Mansson B. Effects on local blood flux of acupuncture stimulation used to treat xerostomia in patients suffering from Sjogren's syndrome. *J Oral Rehab* 1993; **20**: 541–548.
59. Jansen G, Lundeberg T, Kjartansson J, Samuelson UE. Acupuncture and sensory neuropeptides increase cutaneous blood flow in rats. *Neurosci Lett* 1989; **97**: 305–309.
60. Rogers PA, Schoen AM, Limehouse J. Acupuncture for immune-mediated disorders. Literature review and clinical applications. *Probl Vet Med* 1992; **4**: 162–193.
61. Doggrell SA. Migraine and beyond: cardiovascular therapeutic potential for CGRP modulators. *Expert Opin Investig Drugs* 2001; **10**: 1131–1138.
62. Calder JS, Holten I, McAllister RM. Evidence for immune system involvement in reflex sympathetic dystrophy. *J Hand Surg* 1998; **23**: 147–150.
63. Blair SJ, Chinthagada M, Hoppenstedt D, Kijowski R, Fareed J. Role of neuropeptides in pathogenesis of reflex sympathetic dystrophy. *Acta Orthopaed Belg* 1998; **64**: 448–451.
64. Levine JD, Clark R, Devor M, Helms C, Moskowitz MA, Basbaum AI. Intraneuronal substance P contributes to the severity of experimental arthritis. *Science* 1984; **226**: 547–549.
65. Newby DE, Sciberras DG, Mendel CM, Gertz BJ, Boon NA, Webb DJ. Intra-arterial substance P mediated vasodilatation in the human forearm: pharmacology, reproducibility and tolerability. *Br J Clin Pharmacol* 1997; **43**: 493–499.
66. Kashiba H, Ueda Y. Acupuncture to the skin induces release of substance P and calcitonin gene-related peptide from peripheral terminals of primary sensory neurons in the rat. *Am J Chin Med* 1991; **19**: 189–197.
67. Bucinskaite V, Lundeberg T, Stenfors C, Ekblom A, Dahlin L, Theodorsson E. Effects of electro-acupuncture and physical exercise on regional concentrations of neuropeptides in rat brain. *Brain Res* 1994; **666**: 128–132.
68. Ceccherelli F, Gagliardi G, Matteredazzo G, Visentin R, Giron G. The role of manual acupuncture and morphine administration on the modulation of capsaicine-induced edema in rat paw. A blind controlled study. *Acupunct Electrother Res* 1996; **21**: 7–14.
69. Chan WW, Weissensteiner H, Rausch WD, Chen KY, Wu LS, Lin JH. Comparison of substance P concentration in acupuncture points in different tissues in dogs. *Am J Chin Med* 1998; **26**: 13–18.
70. Yonehara N. Influence of serotonin receptor antagonists on substance P and serotonin release evoked by tooth pulp stimulation with electro-acupuncture in the trigeminal nucleus caudalis of the rabbit. *Neurosci Res* 2001; **40**: 45–51.
71. Ma H, Jiang E, Zhao X. The effect of acupuncture on the content of substance P in serum of gravida during delivery. *Zhen Ci Yan Jiu* 1992; **17**: 65–66.
72. Sprott H, Franke S, Kluge H, Hein G. Pain treatment of fibromyalgia by acupuncture. *Rheumatol Int* 1998; **18**: 35–36.
73. Dawidson I, Angmar-Mansson B, Blom M, Theodorsson E, Lundeberg T. The influence of sensory stimulation (acupuncture) on the release of neuropeptides in the saliva of healthy subjects. *Life Sci* 1998; **63**: 659–674.
74. Fu H. What is the material base of acupuncture? The nerves! *Med Hypoth* 2000; **54**: 358–359.
75. Cao X. Scientific bases of acupuncture analgesia. *Acupunct Electrother Res* 2002; **27**: 1–14.
76. Skarda RT, Tejwani GA, Muir WW. Cutaneous analgesia, hemodynamic and respiratory effects, and beta-endorphin concentration in spinal fluid and plasma of horses after acupuncture and electroacupuncture. *Am J Vet Res* 2002; **63**: 1435–1442.
77. Tempfer C, Zeisler H, Heinzl H, Hefler L, Husslein P, Kainz C. Influence of acupuncture on maternal serum levels of interleukin-8, prostaglandin F2alpha, and beta-endorphin: a matched pair study. *Obstet Gynecol* 1998; **92**: 245–248.
78. Petti F, Bangrazi A, Liguori A, Reale G, Ippoliti F. Effects of acupuncture on immune response related to opioid like peptides. *J Trad Chin Med* 1998; **18**: 55–63.
79. Bonta IL. Acupuncture beyond the endorphin concept? *Med Hypoth* 2002; **58**: 221–224.
80. O'Garra A, Barrat FJ. In vitro generation of IL-10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by Th1- and Th2-inducing cytokines. *Immunol Lett* 2003; **85**: 135–139.
81. Jeong HJ, Kim BS, Kim KS, Kim HM. Regulatory effect of cytokine production in asthma patients by SOOJI CHIM (Koryo hand acupuncture therapy). *Immunopharmacol Immunotoxicol* 2002; **24**: 265–274.
82. Petti FB, Liguori A, Ippoliti F. Study on cytokines IL-2, IL-6, IL-10 in patients of chronic allergic rhinitis treated with acupuncture. *J Trad Chin Med* 2002; **22**: 104–111.
83. Wu HG, Zhou LB, Pan YY, Huang C, Chen HP, Shi Z, Hua XG. Study of the mechanisms of acupuncture and moxibustion treatment for ulcerative colitis rats in view of the gene expression of cytokines. *World J Gastroenterol* 1999; **5**: 515–517.
84. Loaliza LA, Yamaguchi S, Ito M, Ohshima N. Electro-acupuncture stimulation to muscle afferents in anesthetized rats modulates the blood flow to the knee joint through autonomic reflexes and nitric oxide. *Auton Neurosci* 2002; **97**: 103–109.
85. Zhao P, Huang ZN, Chen G, Cheng JS. Electro-acupuncture attenuates nitric oxide release from rat striatum after transient middle cerebral artery occlusion. *Acupunct Electrother Res* 2000; **25**: 101–107.
86. Yang R, Huang ZN, Cheng JS. Anticonvulsion effect of acupuncture might be related to the decrease of neuronal and inducible nitric oxide synthases. *Acupunct Electrother Res* 2000; **25**: 137–143.
87. Cirino G, Fiorucci S, Sessa WC. Endothelial nitric oxide synthase: the Cinderella of inflammation? *TIPS* 2003; **24**: 91–95.
88. Linde K, Vickers A, Hondras M, ter Riet G, Thormahlen J, Berman B, Melchart D. Systematic reviews of complementary therapies — an annotated bibliography. Part 1: acupuncture. *BMC Complement Altern Med* 2001; **1**: 3.
89. Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998; **352**: 364–365.
90. Irnich D, Behrens N, Molzen H, et al. Randomised trial of acupuncture compared with conventional massage and 'sham' laser acupuncture for treatment of chronic neck pain. *BMJ* 2001; **322**: 1574–1578.
91. Wu MT, Hsieh JC, Xiong J, et al. Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain — preliminary experience. *Radiology* 1999; **212**: 133–141.
92. White AR, Filshie J, Cummings TM. Clinical trials of acupuncture: consensus recommendations for optimal treatment, sham controls and blinding. *Complement Ther Med* 2001; **9**: 237–245.
93. Birch S, Hammerschlag R, Berman BM. Acupuncture in the treatment of pain. *J Alt Complement Med* 1996; **2**: 101–124.

94. Birch S. Credibility of treatment in controlled trials of acupuncture. *J Alt Complement Med* 1997; **3**: 315–321.
95. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001; **357**: 1191–1194.
96. MacPherson H, White A, Cummings M, Jobst K, Rose K, Niemtzow R. Standards for reporting interventions in controlled trials of acupuncture. The STRICTA recommendations. *Acupunct Med* 2002; **20**: 22–25.
97. Van Houwelingen AH, Kool M, de Jager SC, Redegeld FAM, van Heuven-Nolsen D, Kraneveld AD, Nijkamp FP. Mast cell-derived TNF- α primes sensory nerve endings in a pulmonary hypersensitivity reaction. *J Immunol* 2002; **168**: 5297–5302.
98. Coleman JW. Nitric oxide: a regulator of mast cell activation and mast cell-mediated inflammation. *Clin Exp Immunol* 2002; **129**: 4–10.
99. Brain SD, Hughes SR, Cambridge H, O'Driscoll G. The contribution of calcitonin gene-related peptide (CGRP) to neurogenic vasodilator responses. *Agents Actions* 1993; **38**: C19–C21.
100. Towler PK, Bennett GS, Moore PK, Brain SD. Neurogenic oedema and vasodilatation: effect of a selective neuronal NO inhibitor. *Neuroreport* 1998; **9**: 1513–1518.
101. Brian JE, Faraci FM, Moore SA. COX-2 dependent delayed dilatation of cerebral arterioles in response to bradykinin. *Am J Physiol Heart Circ Physiol* 2001; **280**: H2023–H2029.
102. Zhang L, Hoff AO, Wimalawansa SJ, Cote GJ, Gagel RF, Westlund KN. Arthritic calcitonin/alpha calcitonin gene-related peptide knockout mice have reduced nociceptive hypersensitivity. *Pain* 2001; **89**: 265–273.
103. Tanaka E, Uchiyama S, Nakano S. Effects of calcitonin gene-related peptide and vasoactive intestinal peptide on nicotine-induced sweating in man. *J Auton Nerv Syst* 1990; **30**: 265–268.
104. Kumazawa K, Sobue G, Mitsuma T, Ogawa T. Modulatory effects of calcitonin gene-related peptide and substance P on human cholinergic sweat secretion. *Clin Auton Res* 1994; **4**: 319–322.
105. Kumazawa K, Sobue G, Mitsuma T, Sugeno Y, Ogawa T. Impairment of calcitonin gene-related peptide-induced potentiation of cholinergic sweat secretion in patients with multiple system atrophy. *Clin Auton Res* 1997; **7**: 77–80.
106. Stones RW, Thomas DC, Beard RW. Suprasensitivity to calcitonin gene-related peptide but not vasoactive intestinal peptide in women with chronic pelvic pain. *Clin Auton Res* 1992; **2**: 343–348.
107. Noguchi M, Ikarashi Y, Yuzurihara M, Mizoguchi K, Kurauchi K, Chen JT, Ishige A. Up-regulation of calcitonin gene-related peptide receptors underlying elevation of skin temperature in ovariectomized rats. *J Endocrinol* 2002; **175**: 177–183.
108. Noguchi M, Yuzurihara M, Ikarashi Y. Effects of the vasoactive neuropeptides calcitonin gene-related peptide, substance P and vasoactive intestinal polypeptide on skin temperature in ovariectomized rats. *Neuropeptides* 2002; **36**: 327–332.
109. Spetz AC, Pettersson B, Varenhorst E, Theodorsson E, Thorell LH, Hammar M. Momentary increase in plasma calcitonin gene-related peptide is involved in hot flashes in men treated with castration for carcinoma of the prostate. *J Urol* 2001; **166**: 1720–1723.
110. Kinart CM, Cuppett MM, Berg K. Prevalence of migraines in NCAA division I male and female basketball players. National Collegiate Athletic Association. *Headache* 2002; **42**: 620–629.
111. Silberstein SD. Sex hormones and headache. *Rev Neurol (Paris)* 2000; **156**: S30–S41.
112. Lam N, Thurston A. Association of obesity, gender, age and occupation with carpal tunnel syndrome. *Aust NZ J Surg* 1998; **68**: 190–193.
113. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. *Pain* 2003; **101**: 259–266.
114. Rumsfield JA, West DP. Topical capsaicin in dermatologic and peripheral pain disorders. *DICP* 1991; **25**: 381–387.
115. Ribbers GM, Stam HJ. Complex regional pain syndrome type I treated with topical capsaicin: a case report. *Arch Phys Med Rehab* 2001; **82**: 851–852.
116. Huygen FJPM, Schoneveld JM, Kjaernes J, Niehof S, Klein J, Zijlstra FJ. Capsaicin treatment of a patient with complex regional pain syndrome type 2 results in a clinical improvement. *J Neuroimmunol*. 2003 In press.
117. Gerth Van Wijk R, Terreehorst IT, Mulder PG, Garrelds IM, Blom HM, Popering S. Intranasal capsaicin is lacking therapeutic effect in perennial allergic rhinitis to house dust mite. A placebo-controlled study. *Clin Exp Allergy* 2000; **30**: 1792–1798.
118. Marsh D, Dickenson A, Hatch D, Fitzgerald M. Epidural opioid analgesia in infant rats II: responses to carrageenan and capsaicin. *Pain* 1999; **82**: 33–38.
119. Hua XY, Chen P, Hwang J, Yaksh TL. Antinociception induced by civamide, an orally active capsaicin analogue. *Pain* 1997; **71**: 313–322.
120. Diamond S, Freitag F, Phillips SB, Bernstein JE. Saper Intranasal civamide for the acute treatment of migraine headache. *Cephalalgia* 2000; **20**: 597–602.
121. Saper JR, Klapper J, Mathew NT, Rapoport A, Phillips SB, Bernstein JE. Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol* 2002; **59**: 990–994.
122. Bhardwaj RS, Schwarz A, Becher E, Mahnke K, Aragane Y, Schwarz T, Luger TA. Pro-opiomelanocortin-derived peptides induce IL-10 production in human monocytes. *J Immunol* 1996; **156**: 2517–2521.
123. Hosoi J, Ozawa H, Granstein RD. Beta-endorphin binding and regulation of cytokine expression in Langerhans cells. *Ann NY Acad Sci* 1999; **885**: 405–413.
124. Molina PE. Opiate modulation of hemodynamic, hormonal, and cytokine responses to hemorrhage. *Shock* 2001; **15**: 471–478.
125. Wallengren J. Vasoactive peptides in the skin. *J Invest Dermatol Symp Proc* 1997; **2**: 49–55.

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