



RESEARCH ARTICLE

A Neurovascular Transmission Model for Acupuncture-induced Nitric Oxide

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Abstract

Acupuncture is the practice of inserting needles into the body to reduce pain or induce anesthesia. More broadly, acupuncture is a family of procedures involving the stimulation of anatomical locations on or in the skin by a variety of techniques. Employing acupuncture to treat human disease or maintain bodily condition has been practiced for thousands of years. However, the mechanism(s) of action of acupuncture at the various meridians are poorly understood. Most studies have indicated that acupuncture is able to increase blood flow. The acupuncture points have high electrical conductance and a relationship of the acupuncture points and meridians with the connective tissue planes and the perivascular space has also been suggested. Several studies employing the human and animal models have shown that acupuncture enhances the generation of nitric oxide (NO) and increases local circulation. Specifically, electroacupuncture (EA) seems to prevent the reduction in NO production from endothelial NO synthetase (eNOS) and neuronal NO synthase (nNOS) that is associated with hypertension and this process involves a stomach-meridian organ but not a non-stomach-meridian organ such as the liver. How can we explain the phenomena of EA and meridian effect? Here, we proposed a neurovascular transmission model for acupuncture induced NO. In this proposed model, the acupuncture stimulus is able to influence connective tissue via mechanical force transfer to the extracellular matrix (ECM). Through the ECM, the mechanotransduction stimulus can be translated or travel from the acupuncture points, which involve local tissue and cells. Cells in the local tissue that have received mechanotransduction induce different types of NO production that can induce changes in blood flow and local circulation. The local mechanical stress produced is coupled to a cyclic strain of the blood vessels and this could then change the frequency of resonance. According to the resonance theory, an oscillatory pattern of NO formation might occur in that specific organ. Therefore, the artery tree would then change the blood distribution and microcirculation of various organs and as a result further affect the production of NO.

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1. Introduction

Acupuncture is the practice of inserting needles into the body to reduce pain or induce anesthesia. More broadly, acupuncture is a family of procedures involving the stimulation of anatomical locations on or in the skin by a variety of techniques. Employing acupuncture to treat human disease or to maintain bodily condition has been practiced for thousands of years. Recently, models able to describe the mode of action of acupuncture have aroused scientists' curiosity. Scientific interest in acupuncture has led numerous investigators to conduct clinical trials that have tested the efficacy of acupuncture using various acupuncture points; however, the mechanism(s) of action of acupuncture at the various meridians are still poorly understood.

Previous studies have provided a variety of information regarding the physiological effects of acupuncture on animal and human bodies. Most of them have indicated that acupuncture is able to increase blood flow [1] and that the acupuncture points and meridians have a high electrical conductance [2,3]. A relationship has also been suggested between acupuncture points and meridians with connective tissue planes [4] and the perivascular space [5]. A number of possible mechanisms by which acupuncture acts have been reviewed [6] and these results are available at the site of the National Center for Complementary and Alternative medicine (NCCAM) [7]. A Question and Answer page on "How might acupuncture work?" is also available on the website of the NCCAM at the National Institutes of Health where it states: "It is proposed that acupuncture produces its effects through regulating the nervous system, thus aiding the activity of pain killing biochemicals such as endorphins and immune system cells at specific sites in the body. In addition, studies have shown that acupuncture may alter brain chemistry by changing the release of neurotransmitters and neurohormones and, thus, affecting the parts of the central nervous system related to sensation and involuntary body functions, such as immune reactions and processes that regulate a person's blood pressure, blood flow and body temperature."

The results obtained from human and animal studies have also shown that acupuncture enhances the generation of nitric oxide (NO) and increases local circulation [8]. Kim et al demonstrated that employing acupuncture on stomach 36 point (ST-36) is able to reduce blood pressure by activating NO signaling mechanisms [9]. Ma showed that NO content and NO synthase (NOS) expression were consistently higher at skin acupuncture points/meridians [10]. Chen et al showed that L-arginine-derived NO synthesis appears to mediate the noradrenergic

function of skin sympathetic nerve activation and that this contributes to skin electrical resistance of the acupuncture points and meridians [11].

NO is known to exert an effect on a number of functions including the regulation of blood pressure, contributing to the immune response, the control of neurotransmission and participation in cell differentiation and other physiological functions [12]. NO, a diffusible signaling gas, is synthesized by three NOS isoforms, namely a neuronal NOS (nNOS), an inducible NOS (iNOS) [13] and an endothelial NOS (eNOS) [14,15]. Using BH4 (tetrahydrobiopterin), Ca²⁺-calmodulin, Heme, flavin adenine dinucleotide, riboflavin monophosphate and NADPH [16] as cofactors and coupled with electron transfer, these enzymes are able to convert L-arginine to L-citrulline and NO.

Chinese acupuncture theory maintains that there are twelve main meridians or energy channels that relate to the internal organs. These include the lungs, large intestine, stomach, spleen, heart, the pericardium (the sac around the heart), etc. Electroacupuncture (EA) prevents the reduction of NO production from eNOS and nNOS associated with hypertension and has been shown to even increase eNOS and nNOS expression in stomach and cheek pouch tissue (which are also part of the stomach meridian) compared with a sham control. This effect was found not to occur on liver tissue, a non-stomach-meridian organ [9]. A question arises from the results of this study and this is how to explain the phenomena whereby EA was able to prevent the reduction of NO production from eNOS and nNOS associated with hypertension in a stomach-meridian organ but did not affect a non-stomach-meridian organ. Our hypothesis involves a neurovascular transmission model. Briefly, the acupuncture stimulus is able to induce a burst of NO production through mechanotransduction at the local acupuncture point and this NO diffuses and changes the blood flow either at the local and/or organ microcirculation level. The result of acupuncture is differential production of NO in various meridian organs, which are connected via tissue/cells coupled to the cyclically strained blood vessel; this is able to change the frequency of resonance.

2. A Neurovascular Transmission Model of Acupuncture

In the vascular wall, most of the bioavailable NO is believed to be derived from eNOS and diffuses into vascular smooth muscle and the blood stream, where it rapidly reacts with the hemoglobin (Hb) of the red blood cells. Hb, of course, is also able to transport oxygen and carbon dioxide. The blood

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