In this first installment of a three-part series, "The Art and Science of Traditional Medicine," we present a series of articles making a case for the integration of traditional Chinese medicine (TCM) into modern medical practice. From the new WHO Traditional Medicine Strategy to the application of systems biology in studying TCM, we aim to highlight the potential for creating an integrated, network-based healthcare system. The next two issues will cover herbal genomics and highlight the importance of quality control, standardization, regulation, and safety for traditional treatments. An overview of indigenous medicines in Europe, Africa, the Middle East, India, and the Americas will also be provided.

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L. rhizome, an herb commonly used in Australia to treat symptoms of menopause and rheumatoid arthritis (28), and Leonurus japonicus Houtt., an herb commonly used in TCM for gynecological and obstetric conditions. Additionally, we previously found that ethnobotanical extracts from unprocessed main roots of Aconitum carmichaeli Debx. potent in vitro proliferative activities, which, coupled with the relevant recent consumption of Aconitum species is known to cause acute renal failure and has been recently linked to end-stage renal disease (ESRD) in a case of Chinese Medicine (CM) and Healthcare Products Regulatory Agency (30).

This trend towards growing and avoiding exposure to pro-

fibrotic botanicals is profound. For instance, about one-third of the Taiwanese population consumed AA-containing herbs be-
tween 1997 and 2003 (31) and AAN previously accounted for up to 10% of all ESRD in Taiwan (32). The banning of AA-con-
taining herbs, together with other efforts such as public-aware-
ness campaigns, education of patients, funding for research into chronic kidney disease, and provision of integrated care has turned Taiwan into one of the few regions with retarded increase of ESRD incidence (33).

Moving forward

Due to the contradictory and complex roles botanicals play in fibrotic diseases, there is an urgent need for studies that in-
vestigate the safety, efficacy, and good practices for botanical-
based remedies.

Since fibrotic diseases are multifactorial conditions and botanicals are typically multifaceted targets, an efficacy-based strategy is particularly well-suited for studying anti-fibrotic botanicals.

Such a strategy is highly dependent on disease modeling. It is worth emphasizing that innovation is needed to develop high-quality model systems, so that we can facilitate the investigation of antifibrotics and detect profibrotic activities.

Because evidence-based medicine is a relatively new concept in many countries (34), many clinical reports on herbal treatment of fibrotic diseases are criticized for poor quality. Diseases for which the literature has been recently reviewed include liver fibrosis (25, 35), pulmonary fibrosis (36), multiple sclerosis (37), and chronic obstructive pulmonary disease (37). An
efficacy-based strategy ultimately demands high-quality clini-
cal trials to prove antifibrotic effects and invites interregional cooperation on pharmacovigilance of profibrotic botanicals, which is challenging due to the inidious nature of fibrosis and the variability in the distribution channels and legal status of botanicals in different regions (38, 39).

Finally, traditional use is only an indication but certainly not a proof of either safety or efficacy (40). To harness and under-
stand botanicals both as potential antifibrotic therapies and for the prevention of fibrotic diseases, future research and innovation must focus on efficacy and safety, and must be built on and contribute to good practices, which we have recently defined at length (41). Development and refinement of good practices, however, can only be achieved with substantial funding.

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13. Q. Xu et al., Normokinesins and growth factors in conventional medicine lies in the difficulty of reconciling traditionally defined categories (acupoints, meridians, and energy flow or qi) with anatomical structures and biochemical pathways. Additionally, a unified scientific theory to explain the diverse effects of acupuncture (from pain control to immu-
nomodulation) is lacking, despite important advances in the association of purinergic signaling with the effects of acu-
uncture on pain control. As new technologies simultaneously offer enhanced capacities to explore breadth (using ‘omics’ and depth (using nanobiosips) of biochemical events, we propose the innovative conjunction of these approaches into an intelligent needle (i-needles) as a means to overcome the abovementioned limitations.

Acupuncture is being widely debated in the medical com-
munity as a potential alternative or complimentary treatment for many diseases (1). There are numerous challenges to xiu, X. Liu, N. Hu, G. Q. Wang, Hepatogastroenterology 57, 554 (2010)
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i-Needle: Detecting the biological mechanisms of acupuncture

Authors: Christiane Dasteuret1,2*, Jianbo Zhang1,2,3, Brigitte Guérin1,2, Joaill. Norton1,2

A long standing obstacle to the (full) acceptance and understanding of acupuncture (Acu) as a medical practice is the ability to (re)interpret traditional categories (such as acupoints, meridians, and energy flow or qi) into account distal factors that might play a role in causing or worsening the condition. As such, it is crucial to establish a methodology for building on what has already been reported about the wound healing process, including the presence of peripheral markers of healing (14, 15).

To explore the long range effects of acupuncture, omic-based analysis of molecular events occurring proximally (acupoint), distally from the stimulation point (target organ), and at the site of injury/drug contrast, acupuncture is recommended for systemic diseases like rheumatoid arthritis (17) and is thought to act in a more global fashion.

Using the framework we propose here, we can investigate the long range effects of acupuncture, systemic markers (such as acupoints, me-
idians, and qi) and therapeutic indications with an evidence-
based medicine framework. Important questions arise in in-
creasing our understanding of the molecular effects of needle stimulation have been posed, mostly regarding pain control (2), functional recovery of tissue (3) and immunomodulation (4), although reliable work done as to the correlation of pain control with purinergic signaling (5, 6). Using ‘omics-based technology and network representations, researchers have successfully mapped the molecular signatures of traditional tural categories (7, More generally, the holistic method used in acupuncture (8). The difficulty lies in the requisite temporal and spatial resolution of the data (9). The ability to (re)interpret traditional categories (such as acupoints, meridians, and energy flow or qi) and mechanotransduction are widespread in biology with a variety of approaches to modulate these events. The i-needles can then be enriched with data about the temporal onset of early gene expression, in addition to later time points (Figure 1A) to construct a systems biology view (network) of the biochemical events. To build such networks and identify new targets for diagno-
sis and therapy, computational analysis must bring together the different ‘omics approaches (Figure 1B, coupled with the requisite temporal and spatial resolution of the data (9). This type of network approach can identify the most relevant mole-
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produced by the

systems biology enables the

peripheral bloodstream and

acupuncture treatments lends weight to this hypothesis. ATP

and purinergic signaling in acupuncture

FIGURE 1. Acupuncture and purinergic signaling. Insertion and twisting of the needles employed in acupuncture mechanistically deforms the skin, leading to the release of ATP by skin keratinocytes (1). ATP binds to specific receptors located on sensory nerve endings in the skin, P2X3 and P2X2/3 (2). The signaling message is then relayed via dorsal root ganglia to the spinal cord (3) and subsequently through interneuronal pathways (4) to the brain stem (5) that contains motor neurons, which control the functions of gut, lung, heart, arteries, and reproductive organs—all major targets for acupuncture. Signals also travel to the pain centers of the cortex, delivering a message to inhibit pain (6). Image reproduced with permission from reference 36.

drug

in acupuncture

Author:

Geoffrey Burnstock

he proposed role of purinergic signaling in the physiological basis of acupuncture was first presented in 2009. Data showing that ATP is released from keratinocytes and other skin cells during acupuncture treatments lends weight to this hypothesis. ATP in turn activates P2X3 receptors on the sensory nerves in the skin, which then transmit those messages to motor neurons in the brain stem that control autonomic functions and modulate nociceptive activities. Here, we review and describe the recent evidence for purinergic signaling underlying acupuncture effects and propose ways for further test this hypothesis.

Introduction

It has been well established that adenosine 5’-triphosphate (ATP) is an intracellular energy source in cellular biochemistry. In 1970, Burston et al. suggested that ATP acted as a nonadrenergic, non-cholinergic neurotransmitter in the gut (1). In 1972 he named the extracellular actions of ATP, “purinergic signaling” (since ATP is a purine nucleotide), and formulated the purinergic signaling hypothesis (2).

In 2009, Burston proposed that purinergic signaling could be involved in the physiological mechanisms mediating acupuncture effects. This hypothesis suggested that mechanical deformation of the skin by needles or application of heat or electrical current leads to the release of large amounts of ATP from keratinocytes, fibroblasts, and other cell types in skin (Figure 1). The released ATP then activates P2X3 ion channel receptors on sensory nerve endings in the skin and tongue that transmit messages via sensory ganglia and the spinal cord to the brain stem and hypothalamus. These brain regions contain motor neurons that control autonomic functions, including cardiovascular, gastrointestinal, respiratory, and urinogenital activities—common targets of acupuncture treatments. These sensory neuron messages also modulate the pathways that lead to centers in the cortex responsible for conscious awareness of pain and other central nervous system activities, including skin deep regulation (3). A number of subsequent studies have been published that also implicate purinergic signaling in various aspects of acupuncture, detailed below.

Supporting evidence for the hypothesis

Studies that have established the components involved in the purinergic signaling pathway include: (i) release of ATP (in response to mechanical or chemical stimulation)

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Purinergic signaling in acupuncture

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