

Chronic pain and acupuncture: from needles to analgesia

With millions of people suffering from long-term pain, acupuncture is a popular, but mysterious, alternative to painkilling drugs. Research carried out by **Dr Takahiro Takano**, at the University of Rochester Medical Center, not only sheds light on how acupuncture works – and why it sometimes does not – but may lead to a whole new line of pain-relieving treatments.

Chronic (or persistent) pain, often defined as pain lasting for at least twelve weeks, affects huge numbers of people, including over one-third of the American population. Existing treatments for chronic pain heavily depend on opioid drugs, such as morphine, codeine and tramadol. However, these drugs have disadvantages including side effects, addiction and tolerance, which cause many pain sufferers to turn to alternative treatments, such as acupuncture.

While acupuncture has many devotees, its efficacy has proven hard to document and its success is often highly variable. However, ground-breaking research by Dr Takahiro Takano is beginning to shed light on the physiological basis of acupuncture, and opens up new possibilities for chronic pain treatment that may bridge the gap between conventional and alternative medicine.

PERIPHERAL PAIN RELIEF

Unlike mainstream painkillers, which target the central nervous system (the brain and spinal cord) where pain is perceived, acupuncture targets the peripheral nerves in the rest of the body. Developed in China over 4,000 years ago, it is perhaps the most widely-accepted of all the 'alternative' forms of medicine. Over ten million treatments are carried out each year in the US, with the World Health Organization endorsing it for over two dozen medical conditions. Acupuncture is now even available on the UK's National Health Service.

Acupuncture claims to be a side effect-free form of pain relief – when it works. But so far there is no scientific explanation for its action,

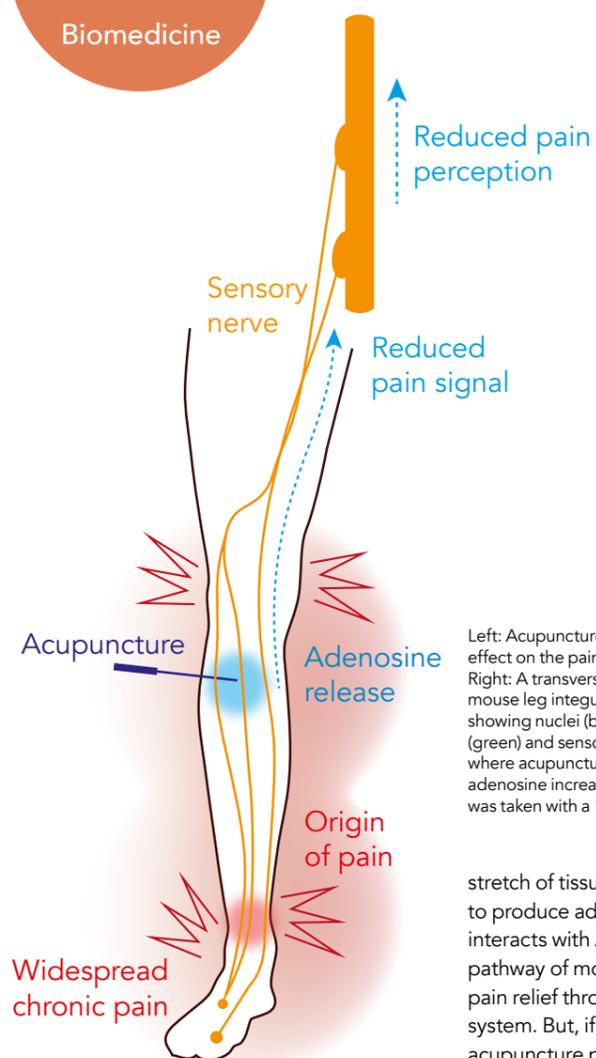
and its effects vary significantly from patient to patient, and even day to day. Some of acupuncture's effects are thought to result from the release of opioid chemicals in the central nervous system, but this by no means explains its entire action, particularly at a more peripheral level. This is where Dr Takano's research comes in. His work at the University of Rochester Medical Center has helped demonstrate not only how acupuncture works, but also why its effects are so unpredictable. His findings may ultimately help improve the efficacy of acupuncture itself, and enable us to exploit its underlying mechanisms in developing new treatments for chronic pain.

Chronic pain may be of two types: inflammatory pain associated with tissue damage, and neuropathic pain associated with nerve damage. Dr Takano's team developed mouse models to characterise both these situations, and showed that acupuncture suppresses both types of pain in these animals. Simultaneously, they found that a small molecule, adenosine, was released at the site of the acupuncture treatment. They later confirmed that the same 'neuromodulator' is released during acupuncture treatment in human patients.

Adenosine was already known to have pain-relieving properties, mediated through receptor molecules called 'adenosine A1 receptors', which are found throughout the human body. Dr Takano's research showed that these A1 receptors are essential for the adenosine released during acupuncture to cause pain relief. He also found that injecting mice with CCPA, a molecule that mimics

The solution for those using acupuncture to treat chronic pain? Lay off the coffee!





Left: Acupuncture's effect on the pain network. Right: A transverse section of mouse leg integumentary tissue showing nuclei (blue), nerve bundle (green) and sensory neurones (red), where acupuncture can induce extracellular adenosine increase. The fluorescence image was taken with a 10x magnification lens.

adenosine's interaction with A1 receptors, brings relief from pain without the need for acupuncture itself. Finally, he showed that inhibiting certain enzymes that degrade adenosine, thus allowing it to build up in the body, could prolong the effect of acupuncture treatment. These findings offer a fascinating insight into an entirely new form of pain relief based around stimulating A1 receptors in the peripheral nervous system.

WAKE UP AND SMELL THE COFFEE...

Dr Takano's research in mice clearly explains how acupuncture works at the molecular level: the insertion and particularly the rotation of acupuncture needles causes localised

stretch of tissue, which stimulates the body to produce adenosine. The adenosine interacts with A1 receptors, initiating a pathway of molecular changes resulting in pain relief throughout the peripheral nervous system. But, if this pathway is clear, why does acupuncture produce such variable results in humans?

Step up one of the most ubiquitous drugs in modern society – caffeine. Present in coffee, tea, chocolate, energy and diet drinks, and some pain medicines, it is estimated that around 90% of the US population consumes caffeine in some form every day. Unfortunately, caffeine also binds to the adenosine A1 receptor, blocking its reception of adenosine and compromising the pain relief pathway. In a paper published last month, Dr Takano and colleagues showed that even very low doses of caffeine interfere significantly with acupuncture's painkilling action. Thankfully, the effect is transient and usually wears off within 24 hours. This phenomenon may well explain why acupuncture sometimes

works and sometimes does not, and suggests an easy solution to those using acupuncture to treat chronic pain: lay off the coffee!

PATHWAY TO PAIN RELIEF

Dr Takano's research does not stop at vindicating acupuncture – he now wants to use his findings to develop new therapies for chronic pain. Aside from further exploring the role of the A1 receptor and the impact of caffeine in mouse models, his latest research project, funded by the US National Institutes of Health, will investigate other ways to manipulate the pain relief pathway that is stimulated during acupuncture treatment.

Acupuncture is not a quick fix therapy: it often provides only a few hours respite, with long-term relief coming only after multiple treatments. However, now that its mechanism of action is known, it may be possible to manipulate the physiological pathways involved to achieve more effective or longer-lasting relief. One potential player in this is an enzyme known as CD73, which can cause the human body to make adenosine from a molecular precursor. Takano's investigations so far suggest that administration of CD73 may contribute to long-lasting, side-effect-free, analgesia, in cases of both inflammatory and neurological, acute and chronic pain.

There is much still to discover but, through Dr Takano's research, we could be on the cusp of a new paradigm for pain relief, bringing hope to many millions of sufferers.

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Q&A

What are the problems with the current 'medical' approach to treating chronic pain?

In a nutshell, side effects and tolerance. Opioids mess up your brain. Steroids affect the reproductive system, growth and other systems. Over-the-counter pain medicines such as non-steroidal anti-inflammatory drugs (NSAIDs) are wonderful, but even they can cause problems in digestive and cardiovascular systems when taken continuously. Many of them are thus unsuitable for patients with multiple medical conditions or during pregnancy. The situation is worsened by the drug tolerance, requiring patients to take a higher dose or switch to another drug.

How did you hit upon adenosine as the key actor in pain relief brought about by acupuncture?

Our research focused on purinergic signalling, cell-to-cell communication via release of ATP and adenosine molecules. We knew that cellular injury or mechanical stress induces purine release, and adenosine is a suppressor of neuronal activity. So the only "jump" we made was to apply the knowledge to peripheral nervous tissue and pain suppression. The needle insertion causes minor injury, and the manual manipulation of the needle causes tissue stretch. It turned out that needle insertion itself was not enough, but that manipulation of the needle induced adenosine increase, mediating the analgesic effect.

How important have animal models been to your research?

Pain is a perception, involving complex stages from different causes of pain and types of pain to the brain's interpretation of sensory signals and psychological state.

By using animal models, we can control the causes and types of pain. At the same time we can exclude the concern of placebo effects, which plays a big role in human acupuncture therapy. The animal model is ideal for dissecting out the biological mechanism of pain suppression.

Do you think acupuncture should still be classed as an 'alternative' medicine – or is it now supported by enough evidence to enter the mainstream?

Both WHO and US NIH recognise acupuncture as a valid pain treatment. Acupuncture is in many states at least partially covered by medical insurance. Right now doctors cannot really predict which patients will get the most benefit from acupuncture. However, every chronic pain patient should be informed about acupuncture as an option for consideration. An effective approach would be for acupuncturists and doctors to exchange information, enabling a tailored therapeutic solution for individual patients.

What remains to be done before this new form of pain relief can enter clinical trials?

We are studying how acupuncture progressively improves the painful condition from immediate but brief suppression to long-lasting relief. Concurrently, we are developing the best way to activate the adenosine-analgesia system to have maximum analgesic effect. Whilst giving CD73 to the acupuncture point prolongs the effect of acupuncture somewhat, it is still invasive. We hope to engineer a better approach, ultimately more effective and reliable than the ancient knowledge of acupuncture, to alleviate chronic pain.

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Detail

RESEARCH OBJECTIVES

Dr Takano's research focuses on developing alternative treatment strategies for chronic pain. His recent research has looked at developing understanding of adenosine signalling – similarly seen when using acupuncture as a therapeutic treatment against chronic pain.

FUNDING

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BIO

Dr Takahiro Takano earned his PhD at New York Medical College, before starting work at University of Rochester focusing on the functions of non-neuronal cells in brain vascular control and tumours. In 2015, Dr Takano moved to Eastman Institute for Oral Health to start his own lab, changing his research focus towards controlling chronic pain.

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