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# An opioid-independent mechanism for acupuncture analgesia: The orexin-endocannabinoid signaling

Acupuncture has been used in traditional Chinese medicine for over 2,500 years and is now recognized worldwide as an effective treatment modality for many disorders, particularly pain relief. The best-known analgesic mechanism of acupuncture is the “endorphin theory”. However, some reports indicated that the pain-relieving effects of acupuncture in patients are not attenuated by naloxone, suggesting other mechanisms mediate acupuncture analgesia. An analgesic mechanism mediated by orexin 1 receptor (OX1R)-initiated cannabinoid 1 receptor (CB1R) signaling in the ventrolateral periaqueductal gray (vlPAG) has been described in a previous study. The present study examines if this mechanism is involved in acupuncture analgesia. We observed that low-frequency electroacupuncture (EA) at the PC6 (Neiguan) acupoint (EA-PC6), but not at a non-acupoint, reduced acute thermal nociceptive responses and neuropathy-induced mechanical allodynia. EA-PC6 increased the number of c-Fos expressing-orexin neurons in the lateral hypothalamus and increased orexin A levels, but lowered γ-amino butyric acid (GABA) levels in the vlPAG. EA-PC6-induced antinociception was significantly attenuated by systemic or intra-vlPAG pretreatment with an OX1 or CB1 receptor antagonist (i.e., SB 334867 and AM251, respectively) and by intra-vlPAG inhibition of the synthesizing enzyme of 2-arachidonoylglycerol (2-AG), but not by systemic pretreatment with opioid receptor antagonists (i.e. naloxone and naltrexone). EA-PC6 elicited a weak antinociceptive effect in Cnr1-/- mice, which lack CB1 receptors. Directly stimulating the surgically exposed median nerve also increased vlPAG orexin A levels, while a proximal block of the median nerve with lidocaine prevented EA-PC6-induced antinociception. These findings suggest that EA-PC6 stimulated the median nerve to activate hypothalamic orexin neurons and thus induce analgesia through an opioid-independent, but CB1 receptor-dependent cascade, mediated by OX1 receptor-initiated retrograde disinhibition of 2-AG release in the vlPAG.

## ABOUT THE SPEAKER

Dr. Yi-Hung Chen is a Professor and Associate Dean at the Graduate Institute of Acupuncture Science, College of Chinese Medicine, China Medical University in Taichung, Taiwan. Dr. Chen obtained his Ph.D. from the College of Medicine at National Taiwan University. He has ever been serving as the Visiting Scholar at the Department of Pharmacology, Temple University School of Medicine, Philadelphia, U.S.A. Nowadays. Dr. Chen focused his research on the effects of acupuncture relating to analgesia and neuroprotection. His recent study concerns the non-opioid acupuncture analgesia mechanisms, which was published in Proceedings of the National Academy of Sciences of the United States in 2018.

Tuesday
2 July 2019
10.30am – 11.30am
Seminar Room, MD10
Level 2, Anatomy Museum

**Yi-Hung Chen**

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