CHAPTER 31

ACUPUNCTURE AS A VIABLE TREATMENT FOR VISCERAL PAIN

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SUMMARY

Visceral pain, a type of pain originating from the abdominal, thoracic, pelvic, and abdominal organs, is markedly different from somatic or neuropathic pain as it is diffuse and poorly localized and leads to an impact on the patient's quality of life. Acupuncture, a Chinese healing practice, has gained enormous popularity among clinicians for the treatment of visceral pain in recent years. This chapter aims to elaborate on the efficacy and potential of acupuncture as a treatment for the alleviation of visceral pain. The chapter begins with an overview of visceral pain, its impact on the quality of life, and an overview of acupuncture. The etiology, characteristics, predisposing factors, and indications for visceral pain are discussed. The Peripheral and central sensitization include the sensitization of visceral afferent fibers and, the release of inflammatory mediators and neurotransmitters. We also discussed the pharmacological approach for the treatment of visceral pain, its side effects, and acupuncture as a viable treatment for visceral pain. In conclusion, the results of earlier research on the neurological and chemical alterations that occur along the brain-gut axis in people and animals to shed light on the fundamental mechanisms influencing how acupuncture treats visceral pain were shown. The findings presented in this chapter showed that acupuncture treatments significantly reduced visceral pain. This chapter acknowledged further research on the mechanism behind acupuncture analgesia on visceral pain.

INTRODUCTION

Visceral pain is a type of pain arising from the organs of the chest, pelvic or abdominal area due to inflammation, tumors or intestinal dilation (Luo et al., 2023). Visceral pain contributes significantly to morbidity and quality of life deterioration (Wie et al., 2022). Compared to somatic pain, visceral pain has various characteristics for example visceral pain is diffuse, rarely associated with actual injuries, and is not provoked by all of the viscera (Bielefeldt & Gebhart 2022). Curiosity in the factors and mechanisms that are involved in the etiology of visceral pain is expanding. Etiologies of visceral pain include activated visceral nociceptors mechanically or chemically through a variety of underlying diseases including inflammation, ischemia, intestinal distension and cancer (Wie et al., 2022). hypersensitive visceral nociceptors (visceral hypersensitivity), impaired gut-brain axis, genetic and environmental factors, infections, and psychological distress are also contributing factors (Cervero, 2014). Furthermore, a significant advancement in our understanding of human central and peripheral mechanisms and the intestinal environment such as microbiota, has led us to hypothesize that the brain-gut axis, which regulates neuronal and chemical transmission between the gastrointestinal tract and the brain, plays a critical role in visceral nociception. Abdominal pain in inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), which are organic and functional forms of visceral pain, is caused by one of the most contributing factors visceral hypersensitivity (VH) (Tahir et al., 2021). It can be defined as when a person is exposed to colorectal distension (CRD), he may perceive hypersensitive visceral pain. Patients who have IBS or IBD have a predictable development of VH. The medications used for the

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curement of visceral pain include Anti-inflammatory, Antispasmodics, Antidepressants, and opioids. However, the long-term use of these drugs is associated with a number of side effects including intolerance, less pain relief, gastrointestinal and cardiovascular toxicities, peptic ulcer (Bindu et al., 2020) and opioid induced bowel dysfunction (OIBD).

The oldest Chinese medical technique, acupuncture, has been utilized to treat abdominal discomfort as well as a variety of pain disorders. It has shown to be quite effective at reducing pain, with very rare cases of side effects. Numerous studies have examined the general pain-relieving effects of acupuncture, and it is reported that these effects are primarily achieved by controlling the levels of serotonin, endogenous opioids, and norepinephrine as well as by blocking inflammatory cytokines, visceral nociceptors, and CNS activation (I.-S. Lee et al., 2019). Acupuncture can reduce visceral hypersensitivity, Enteric nervous system (ENS) activation (Hu et al., 2015), and brain-gut axis modulation (Li et al., 2015). Acupuncture is the process in which acupoints are stimulated through the insertion of tiny needles and manipulated through manual, electrical, or other forms of stimulation. The practice of electroacupuncture (EA), in which the needles are attached to an electrical stimulator that sends either high-frequency or low-frequency impulses, or a combination of both, was developed in the 1950s. EA has been standardized in terms of electrical stimulation frequency, voltage, waveform, and duration. Nevertheless, in the majority of clinical investigations, manual acupuncture is regarded as the standard therapy.

DEFINING VISCERAL PAIN

A major paradigm change in the understanding of the scope and significance of visceral pain diseases can be seen in the current increase in curiosity among academics and physicians in pain coming from visceral organs. The majority of people have had pain in their internal organs, which can range from minor discomfort from indigestion to excruciating pain from renal colic. Females are also prone to numerous types of visceral pain linked to procreative life. Internal organ pain is referred to as visceral pain, which is diffuse and poorly localized. Visceral pain has the interesting characteristic of frequently "referring" to somatic areas or organs that are not the actual cause of pain. In contrast, in other visceral pain diseases like IBD and functional dyspepsia, no structural or histological anomalies are shown to be the cause of the pain. Visceral pain is a defining characteristic of numerous illnesses, some of which have specific organ pathophysiologies like IBD, pancreatitis, and gynecological pain. However, pain arising from the abdomen is one of the most common reasons for patients to look for medical assistance (Molus & Kansal 2022).

Etiology of visceral pain

The basic causes of visceral pain include visceral hypersensitivity (sensitized visceral nociceptors), gut-brain axis impairment, Infections, Psychological factors, Genetic factors, Hormonal changes, Inflammation, Distention, and ischemia. Hallow organs like the colon are vulnerable to both inflammation and luminal distention but not to burning or cutting(I.-S. Lee et al., 2019).

Characteristics of visceral pain

Since the parenchyma of the liver, kidney, and lungs are not responsive to pain, it does not originate from all of the organs. It need not always be related to injury, for instance, cutting the intestines does not cause pain. It is poorly localized. Autonomic and motor reactions like nausea, vomiting, and tension in the lower back muscles accompany visceral pain. It is referred to other locations (Schwartz & Gebhart 2014).

Pre-disposing factors of visceral pain

The most common conditions underpinning the perception of visceral pain are functional gastrointestinal disorders (FGID). The hallmark GI symptoms of FGID must be present for at least three months without any clear organic etiology in order to be identified. IBS, which affects 1.1-29.2% of the general people, and accounts for a considerable share of stomach discomfort and pain in patients looking for medical assistance, is included in this. Another characteristic that sets IBD apart is visceral pain, which affects 30–50% of people with no apparent inflammation during remission and relapse of the illness. Although pain can be initially caused by the activation of pro-inflammatory cytokines that sensitize primary afferent sensory neurons, visceral hypersensitivity, which can remain after inflammation and after remission, is much harder to comprehend. Visceral hypersensitivity in these circumstances is defined by (Najjar et al., 2020), as continuing even 4-6 weeks after recovery and in the absence of evident inflammation. The need for appropriate animal models is evident given the prevalence of gastrointestinal-related pain syndromes and the fact that much remains unknown about the etiology and pathophysiology of pain, especially when it manifests without clear biological indicators (Pacheco-Carroza, 2021).

Clinical indications of visceral pain

The clinical characteristics of visceral pain typically change over time and depend on the stage of pathology. The sensation known as "true visceral pain" is widespread and ill-defined, and it is typically felt in the upper belly or lower sternum, along the body's midline. Visceral pain is diffuse and poorly localized, in terms of timing and location, and felt more broadly than painful cutaneous stimuli. Following the initial onset of symptoms,

parietal somatic organs in the same metameric field as the afflicted organ may experience referred pain. Viscero-somatic convergence causes deep or superficial body wall tissues to experience secondary hyperalgesia as a result of spatial discrimination of visceral pain being transferred to superficial structures. Referred pain, whether it is accompanied by hyperalgesia or not, is more acute, more precisely localized, and less likely to be accompanied by autonomic symptoms, making it more difficult to distinguish from pain with somatic origins. Visceral pain is frequently accompanied by prominent autonomic symptoms, such as pallor, excessive sweating, nausea, GI problems, and changes in body temperature, blood pressure, and heart rate (Sikandar & Dickenson 2012).

ANIMAL MODELS OF VISCERAL PAIN

Given the complexity of the condition, it is incredibly challenging to create an animal visceral pain model that can faithfully represent all aspects of functional visceral pain. Rats and mice have been used to produce the vast majority of visceral hyperalgesia animal models. One may distend the hollow organs to observe the reflex of abdominal muscle contraction or autonomic responses (change in the cardinal parameters). These techniques have been used to evaluate visceral pain in the stomach, colon, gall bladder, ureter, and urinary bladder. The visceral organs are either chemically inflamed or the animals are stressed early on to cause hyperalgesia (Wesselmann et al., 2009).

Inflammatory model

Inflammatory agents, such as Trinitrobenzene sulfonic acid (TNBS), colitis and cystitis induced by zymosan, and esophagitis, induced by infusion of acid, cyclophosphamide, are injected into the viscera to produce the most often used inflammatory models. Although these inflammatory models cannot be regarded as accurate representations of nonpathological functional visceral pain in a strict sense, the animals' hyperalgesia may closely reflect the characteristics of discomfort experienced by patients. Rats exhibit symptoms resembling ulcerative colitis when haptens such as TNBS are injected into their colon. The inflammation reaches its height four to five days after the injection and lasts for roughly 30 days.

Stress model induced by neonatal maternal separation

Early neonatal development is crucial for the neural nociceptive pathways, as they need use-dependent activity to function normally. Still, aberrant stimuli like stress, chronic pain, or inflammation during the newborn period may have a negative effect on development and ultimately result in reduced pain thresholds in adulthood. The newborn maternal separation (MS)-induced stress paradigm was created with the aim of analyzing the impact of early-life stress on the development of visceral hypersensitivity when inflammation is not present. The model may reflect a portion of IBS patients who have had traumatic events in the past, including sexual, physical, and emotional abuse as well as a life-threatening state in infancy. The postnatal period in rats, from day 2 (P2) to day 14 (P14), is crucial for the development of the nervous system. Numerous studies have suggested that neonatal MS alters neuroendocrine and neuropeptide production over the long run by causing hypothalamic-pituitary-adrenal axis dysregulation (West & McVey Neufeld 2021).

THE MECHANISMS BEHIND VISCERAL PAIN

The pathophysiology of visceral disorders involves several pathways at the peripheral, spinal, and supraspinal sites. Sensitization of peripheral or central pathways, which can be impacted by a number of events, leads to visceral hypersensitivities, such as stress, mood, and chronic inflammation. Visceral hypersensitivity increases the experience of luminal stimuli. Additionally, due to receptor polymorphisms, neurotransmitter receptors, or reuptake processes, some people are more susceptible to chronic pain or more resilient to it.

Peripheral sensitization

Viral antigens, poisons, and byproducts of microbial fermentation can pass through the epithelial barrier and stimulate afferent nerve endings, causing visceral afferent sensitization, when epithelial permeability is increased. Additionally, due to immune mediators secreted at the site of injury, inflammation causes long-term changes in the physiology of the afferent terminals. Visceral pain can be directly caused by afferent terminal sensitization by inflammatory mediators. Neurotransmitters such as substance P, calcitonin gene-related peptide, and nitric oxide are released at the site of an acute injury, where mediators such as cytokines, prostaglandins, and histamine activate receptors on afferent terminals to increase intracellular second messengers. These neurotransmitters can further sensitize visceral afferents. Protein kinases A and C, the second messenger systems, also alter gene expression, which promotes neuronal plasticity and alters the expression of receptors.

Central sensitization

Neuronal remodeling occurs as a result of pain sensitization in the spinal cord's dorsal horn. The primary visceral afferent releases glutamate at the level of the superficial lamina of the spinal cord to activate a second-order neuron, which then activates AMPA receptors and NMDA receptors. Algesic mediators are also released by primary afferents, including

substance P, which triggers second messenger signaling to start neuronal remodeling and alters the characteristics of the receptors found in the second-order neuron's dendritic structure. In response to the main nociceptor's ongoing activation of the second-order neuron, the dendrites undergo a phenotypic switch that increases the expression of a calcium-permeable version of the AMPA receptor, increasing the excitability of the second-order neuron. The release of neurotransmitters from the primary nociceptive afferent activates presynaptic receptors on the inhibitory interneuron, resulting in hyperpolarization of the inhibitory interneuron and a decreased release of gamma-aminobutyric acid (GABA) and/or glycine onto the second-order neuron at the level of the spinal interneurons. Thus, a sustained hyperexcitable condition in the second-order system can result from enhanced excitation and disinhibition. Thus, a sustained hyperexcitable state in the second-order neuron and persistent nociceptive transmission can result from a combination of enhanced excitation and disinhibition (Lee et al., 2019).

Predominant receptors, channels, and mediators of visceral pain

The channels which are important to the onset of visceral pain include transient receptor potential vanilloid-1 channel (TRPV1), acid-sensing ion channel (ASIC3), voltage-gated sodium channel (NA), voltage-gated calcium channel (CA), and ATP-Gated ion channels (Davis, 2012).

The common forms of visceral pain include irritable bowel syndrome, which is a digestive illness characterized by crampy abdominal discomfort, Inflammatory bowel disease, vulvodynia, persistent vulva pain, bladder discomfort (cystitis), and pain in the prostate (prostatitis)

TREATMENT FOR VISCERAL PAIN

Analgesics (non-steroidal anti-inflammatory drugs), opioids, antispasmodics, and antidepressants are among the medications used to alleviate visceral pain. However, prolonged use of these medications can have a number of negative effects, such as peptic ulcers, inadequate pain management, and toxicities to the gastrointestinal and cardiovascular systems (Davis, 2012). NSAIDs are cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX- II) selective inhibitors. (Brzozowski et al., 2001). Long-term inhibition of COX1 may result in a severe gastrointestinal disorder like peptic ulcer and the long-term inhibition of COX2 may cause cardiovascular toxicities (Drazen, 2005). The use of CAM may be influenced by a number of reasons, including the chronic nature of IBD, the growing interest in and use of CAM generally, or a specific trend in this patient population. Surveys stated that 47% of the people suffering from IBD used some sort of alternative treatment in Canada and 51% in the U.S. (Langhorst, 2005).

Acupuncture as a viable treatment for visceral pain

One of the oldest Chinese medical modalities, acupuncture has been used for more than 3000 years to treat both humans and animals. One of the mainstays of traditional Chinese medicine, acupuncture is often utilized for pain relief. Stress reduction is one aspect of total wellness that is being used more and more. Acupuncture is described in traditional Chinese medicine as a tool to control the flow of qi, chi, or chee, which is believed to move through your body along meridian routes. According to the acupuncture principle, energy flow can be balanced again by putting needles at certain points along these meridians. In contrast, many Western practitioners believe that acupuncture needles are places where muscles, connective tissue, and nerves can be activated. These days, Chinese medicine has convinced modern Western medicine of its similarities.

The way acupuncture works to relieve visceral pain

Numerous studies have demonstrated that acupuncture largely reduces pain by regulating the endogenous opioid system, norepinephrine, and serotonin. It also inhibits the activation of the central nervous system by limiting the release of inflammatory cytokines and visceral nociceptors (Wan et al., 2017). Acupuncture can also reduce visceral pain, stimulate gut ENS, and modulate the gut-brain axis. Electro-acupuncture (EA), a modern version of acupuncture has widely been studied for its effectiveness in relieving VH. It stimulates the peripheral nerves by the given electric stimulation through the inserted needles at specific acupoints. One can easily standardize the wavelength, frequency, and voltage of the stimulation to be given. A variety of types of peripheral afferent innervation can be excited by different EA intensities, which can result in varying degrees of analgesia. Depending on how strong the electric stimulation is, EA can prevent the transmission of visceral nociception. The opioid receptors μ and δ mediate the analgesic effects of EA at a lower frequency of 2 Hz. It delivers the analgesic action via κ-opioid receptor mediation at 100 Hz. (Han, 2004). It stimulates the release of peptides of opioid endogenous system endorphins, dynorphins, and encephalin at the same frequency. EA reduces the levels of acetylcholine (Ach) (Yang et al., 2019) and substance P to relieve visceral pain (Liu, 2010). Pro-inflammatory cytokines like IL-6 β, IL-1, and TNF-α have been reduced after the application of EA in an experimental model of TNBS-induced colitis (Tian, 2003).

Peripheral mechanism of acupuncture

Both central and peripheral pathways contribute to the etiology of visceral pain. Previous studies have demonstrated

the critical role that a range of deleterious stimuli play by altering the enteric mucosal lining's receptors. This triggers mast cell activation and the release of several inflammatory mediators, including prostaglandins and bradykinin, which subsequently act on the corresponding receptors of the sensory nerve endings. Consequently, nociceptive signals are sent to the spinal cord. Visceral pain is lessened by acupuncture's control of a variety of peripheral neurobiological chemicals, including peptides, neurotransmitters, and cytokines. In the intrinsic neural system, cholinergic neurons in the intestinal myenteric plexus and submucosal nerve plexus emit Ach, an important neurotransmitter. Ach, which is recognized as a crucial neurotransmitter for regulating GI motility and a strong regulator of intestinal function, is one of the main afferents of the acupuncture analgesic mechanism. By lowering the Ach level, which rises in response to inflammatory processes, acupuncture may reduce the visceral pain response.

The central mechanism of acupuncture

Studies show that visceral pain is associated with the excitation of different neurotransmitters in the spinal cord. The bodies of nociceptors from the peripheries and the nerves descending from the brain form a network in the dorsal horn of the spinal cord. The transmission of nociceptive information from the spinal cord to the brain occurs through a variety of ion channels, neuromodulators, and receptors. Visceral pain can be alleviated by inhibiting these ion channels, neuromodulators, and receptors at the spinal level. The neuronal responses that are triggered as a result of activation of enteric nociceptors can be inhibited through acupuncture stimulation alleviation of pain can be brought.

EA significantly increases the release of endogenous opioids which suppress the levels of different neurotransmitters responsible for pain sensitization at the dorsal root ganglion and exert an analgesic effect. Another biological hallmark for the examination of neuronal activity is c-Fos as it can cause the excitation of CNS when its levels increase in the spinal cord and contribute to the generation of pain. EA significantly reduces the expression of c-Fos in the spinal cord bringing analgesia. One of the important signaling mechanisms for the sensitization of CNS is the Janus kinase (JAK) signal transducer and activator transcription (STAT) pathway which can be activated by cytokines. It is involved in the transduction of visceral pain. One of the pro-inflammatory cytokines of this pathway is IL-6. Studies show that EA reduced JAK/STAT and the levels of IL-6 bringing analgesia. In order to alleviate visceral pain, a prior study showed that EA could control the expression of P2X3 receptors in both the peripheral and central pathways of visceral pain transmission. P2X3 is found to transmit nociceptive information from the peripheries to the brain (Weng et al., 2015).

CONCLUSION

Acupuncture is a Chinese healing practice that is thought to be used to heal pain originating from our organs. Studies have indicated that it can lower pain and enhance the standard of living for those suffering from IBS, IBD, endometriosis, and chronic pancreatitis. There are several routes by which acupuncture reduces visceral pain, ranging from the gut to the central nervous system (brain). Visceral pain originates in the visceral organs and acupuncture directly controls visceral pain by raising endogenous opioid neurotransmitter and serotonin levels while lowering intrinsic inflammatory biomarker levels. Acupuncture-induced neural impulses go from the spinal cord to the brain, where they reduce the levels of inflammatory biomarkers like p38, P2X3, and NR2B in the spinal cord as well as peripheral neuronal activity. The brain's neural activity and levels of pain-excitatory neurons are decreased by acupuncture, and the levels of stress-related hormones are also decreased. This suggests that the neural and hormonal changes in the thalamus and hypothalamus are responsible for the pain-moderating effects of acupuncture on visceral pain. Additionally, β-endorphin and pain inhibitory neurons, which are also linked to pain inhibition, are elevated after receiving acupuncture. Though the exact mechanism of action is unknown to scientists, it is thought to function by stimulating specific body sites, which in turn modulates nerve activity and lowers inflammation. This chapter outlines the results of earlier research on the neurological and chemical alterations that occur along the brain-gut axis in people and animals in order to shed light on the fundamental mechanisms influencing how acupuncture treats visceral pain. The findings presented in this chapter showed that acupuncture treatments significantly reduced visceral pain. It will take time to fully comprehend the mechanism underlying acupuncture's effects on visceral discomfort, though. Although there is still much to learn, the data suggests that it is a safe method of managing visceral pain.

REFERENCES

Bielefeldt K & GF Gebhart, 2022. Visceral pain. In: Clinical Pain Management: A Practical Guide (Lynch ME, KD Craig & PW Peng, eds): Wiley Blackwell, Oxford, UK, pp. 355-365.

Bindu S, S Mazumder & U Bandyopadhyay, 2020. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical Pharmacology 180:114147.

Brzozowski T, PC Konturek, SJ Konturek, Z Sliwowski, R Pajdo, D Drozdowicz, A Ptak & EG Hahn, 2001. Classic NSAID and selective cyclooxygenase (COX)-1 and COX-2 inhibitors in healing of chronic gastric ulcers. Microscopy Research and Technique 53:343-353.

Cervero F, 2014. Pathophysiology of visceral pain. Revista Dor 15:133-138.

Davis MP, 2012. Drug management of visceral pain: concepts from basic research. Pain Research and Treatment 2012:265605.

Drazen JM, 2005. COX-2 inhibitors--a lesson in unexpected problems. New England Journal of Medicine 352:1131-1132.

Han JS, 2004. Acupuncture and endorphins. Neuroscience Letters 361:258-261.

Hu S, Z-K Zhao, R Liu, HB Wang, CY Gu, HM Luo, H Wang, MH Du, Y Lv & X Shi, 2015. Electroacupuncture activates enteric glial cells and protects

the gut barrier in hemorrhaged rats. World Journal of Gastroenterology 21:1468-1478.

Langhorst J, IB Anthonisen, U Steder-Neukamm, R Lüdtke, G Spahn, A Michalsen & GJ Dobos, 2005. Amount of systemic steroid medication is a strong predictor for the use of complementary and alternative medicine in patients with inflammatory bowel disease. Results from a German national survey. Inflammatory Bowel Diseases 11:287-295.

Lee IS, S Cheon & JY Park, 2019. Central and peripheral mechanism of acupuncture analgesia on visceral pain: a systematic review. Evidence-based Complementary and Alternative Medicine 2019:1304152

Li H, T He, Q Xu, Z Li, Y Liu, F Li, B-F Yang& C-Z Liu, 2015. Acupuncture and regulation of gastrointestinal function. World Journal of Gastroenterology 21:8304-8313.

Liu JH, WB Fu, ZH Xu, Y Liao & X-R Li, 2010. Effect of transection or pretreatment of the infraorbital nerve with snake venom on the analgesia induced by electroacupuncture of" Sibai"(ST 2) acupoint in visceral pain rats. Zhen Ci Yan jiu = Acupuncture Research 35:281-286.

Luo HM, JR Ye & FQ Pu, 2023. Role and therapeutic target of P2X2/3 receptors in visceral pain. Neuropeptides 101:102355.

Molus L & A Kansal, 2022. Visceral pain. Anaesthesia and Intensive Care Medicine 23:535-539.

Najjar SA, BM Davis & KM Albers, 2020. Epithelial-neuronal communication in the colon: implications for visceral pain. Trends in Neurosciences 43:170-181.

Pacheco-Carroza EA, 2021. Visceral pain, mechanisms, and implications in musculoskeletal clinical practice. Medical Hypotheses 153:110624.

Schwartz ES & G Gebhart, 2014. Visceral pain. In: Behavioral Neurobiology of Chronic Pain, Current Topics in Behavioral Neurosciences (Taylor B & D Finn eds) Springer, Berlin, Heidelberg pp. 171-197.

Sikandar S & AH Dickenson, 2012. Visceral pain: the ins and outs, the ups and downs. Current Opinion in Supportive and Palliative Care 6:17-26.

Tahir AH, J-J Li & Y Tang, 2021. Peripheral and spinal mechanisms involved in electro-acupuncture therapy for visceral hypersensitivity. Frontiers in Neuroscience 15:696843.

Tian L, YX Huang, M Tian, W Gao & Q Chang, 2003. Downregulation of electroacupuncture at ST36 on TNF-α in rats with ulcerative colitis. . World Journal of Gastroenterology 9:1028-1033.

Wan J, Y Ding, AH Tahir, MK Shah, H Janyaro, X Li, J Zhong, V Vodyanoy & M Ding, 2017. Electroacupuncture attenuates visceral hypersensitivity by inhibiting JAK2/STAT3 signaling pathway in the descending pain modulation system. Frontiers in Neuroscience 11:644.

Weng Z, L Wu, C Zhou, C Dou, Y Shi, H Liu & H Wu, 2015. Effect of electroacupuncture on P2X 3 receptor regulation in the peripheral and central nervous systems of rats with visceral pain caused by irritable bowel syndrome. Purinergic Signalling 11:321-329.

Wesselmann U, AP Baranowski, M Börjesson, NC Curran, PP Czakanski, MA Giamberardino, TJ Ness, MT Robbins & RJ Traub, 2009. Emerging therapies and novel approaches to visceral pain. Drug Discovery Today: Therapeutic Strategies 6:89-95.

West C & KA McVey Neufeld, 2021. Animal models of visceral pain and the role of the microbiome. Neurobiology of Pain 10:100064

Wie C, S Ghanavatian, S Pew, A Kim, N Strand, J Freeman, M Maita, S Covington & J Maloney, 2022. Interventional treatment modalities for chronic abdominal and pelvic visceral pain. Current Pain and Headache Reports 26:683-691.

Yang J, B Shang, H Shi, S Zhu, G Lu & F Dai, 2019. The role of toll-like receptor 4 and mast cell in the ameliorating effect of electroacupuncture on visceral hypersensitivity in rats. Neurogastroenterology and Motility 31:e13583.