Saik J. Acupuncture: from pain management to regenerative medicine.
Am J Trad Chin Vet Med 2024; 19(2):1-2. https://doi.org/10.59565/001c.121501

Editorial

Acupuncture: From Pain Management to Regenerative Medicine

Acupuncture, widely recognized for its effectiveness in alleviating pain, has been integrated into standard pain management protocols in both human and veterinary medicine.[1,2] This modality plays a critical role in traditional Chinese veterinary medicine (TCVM), where the Kidney/ Water Element, embodying the concept of Prenatal *Jing* (Essence), is believed to be pivotal in the development of embryos, bone marrow, and stem cells. Conventional medical research has recently broadened our understanding of the ancient concept of Essence/*Jing*. Significant findings have come to light on acupuncture's potential to impact the body's stem cells, which are vital for tissue repair and regeneration.

Interest for research in this area was sparked in 2011 when Dr. Maria Grant, University of Alabama Medical School faculty, sought acupuncture treatment from Dr. Huisheng Xie, Chi University faculty, for her 13-year-old Oldenburg gelding, who had sustained a suspensory ligament injury during Prix St. Georges dressage training. Following six sessions of electro-acupuncture (EAP), administered bi-weekly, not only did the gelding's suspensory ligament completely heal, but he also returned to regular dressage training. Intrigued by the remarkable recovery and curious about the underlying mechanism(s) of acupuncture that promoted ligament healing following injury; Dr. Grant was motivated to explore this therapeutic modality further. Consequently, she proposed a collaborative research project with Dr. Xie to investigate whether acupuncture could activate signaling pathways that could mobilize stem cells from tissue niches such as the bone marrow, fat, and perivascular regions into the bloodstream.

The findings from their research on horses suggested that EAP stimulation could facilitate the release of mesenchymal stem cells (MSCs) into the peripheral circulation, with the levels of MSC increasing 300% over baseline at peak response which was typically 2 hours but could last up to 6 hours. Further studies demonstrated that the EAP activated peripheral blood derived MSC could be easily expanded *ex vivo* and readministered therapeutically to horses with degenerative arthritis as well as acute injury. These groundbreaking results not only garnered additional funding but also attracted interest from the wider scientific community, extending research into humans, mice, and rats. Following six years of rigorous research conducted by a team of over 40 scientists, their collective findings were published in the esteemed journals, *Stem Cells* and *PLoS One*.[3,4]

Initial findings demonstrated acupoint stimulation using EAP at LI-4, LI-11, GV-14 and *Bai-hui* resulted in mobilization of MSC into the systemic circulation, and this was uniform across 4 species (humans, horses, and rodents). Further experiments showed that EAP at remote sites produced powerful long-lasting analgesia, modulated cytokine production, and enhanced tissue reorganization in tendon injury models through increased generation of mature type I collagen fibers versus thinner, immature type III fibers. While EAP's analgesic capabilities have been well accepted, the ability of this treatment modality to release reparative cell populations was unknown. Studies using fMRI in humans and rats, investigating the underlying mechanism for this effect, noted hypothalamic activation by EAP. The hypothalamus contains neurons with important projections to the sympathetic nuclei which directly communicate with the periphery. Investigators suggested the mechanism of action was centrally mediated through hypothalamic activation by EAP which amplifies sympathetic nervous system activity, leading to mobilization of MSC into the circulation providing enhanced tissue repair and analgesic relief.

This research result opens up intriguing possibilities for enhancing the body's natural healing processes without any pharmaceutical medications. In the context of injuries, EAP can accelerate recovery by boosting the availability of stem cells in the affected area. Similarly, in degenerative conditions or age-related decline, EAP might offer a novel approach to stimulate the body's regenerative mechanisms, potentially improving outcomes in diseases that currently have limited treatment options.

It's important, however, to approach these findings with cautious optimism. While this research is promising, there is a need for additional studies to fully understand the mechanisms at play, the optimization of stem cell mobilization, and the clinical implications of these effects. Questions remain regarding the most advantageous EAP protocols, including frequency and duration of electrical stimulation and acupoint selections for different types of injuries, degenerative conditions, and individual patient constitutions that may influence outcomes. As we continue to explore the nexus between acupuncture and stem cell biology, it is crucial to maintain rigorous scientific standards. Collaboration between TCVM clinicians and biomedical researchers can facilitate a deeper understanding of acupuncture's potential benefits, ensuring that claims are supported by solid evidence.

In conclusion, the exploration of acupuncture's role in releasing MSC represents a compelling convergence of ancient wisdom and cutting-edge science. As research advances, there is hope that this traditional practice could offer innovative solutions to some of modern medicine's most challenging problems, illuminating a path toward harnessing the body's innate capacity for healing and regeneration.

Respectfully Submitted,
Judith E Saik DVM, DACVP
Editor-in-Chief, AJTCVM

REFERENCES

1. Patil S, Sen S, Bral M et al. The role of acupuncture in pain management. Curr Pain Headache Rep 2016; 20(4):22. https://doi.org/10.1007/s11916-016-0552-1
2. Huntingford J, Petty M. Evidence-based application of acupuncture for pain management in companion animal medicine. Vet Sci 2022; 9(6):252. https://doi.org/10.3390/vetsci9060252
3. Salazar T, Richardson M, Beli E et al. Electroacupuncture promotes central nervous system-dependent release of mesenchymal stem cells. Stem Cells 2017; 35(5):1303-1315. https://doi.org/10.1002/stem.2613
4. Longhini A, Salazar T, Vieira C et al. Peripheral blood-derived mesenchymal stem cells demonstrate immunomodulatory potential for therapeutic use in horses. PLoS One 2019; 14(3):e0212642. https://doi.org/10.1371/journal.pone.0212642

ABSTRACT

Salazar T, Richardson M, Beli E et al. Electroacupuncture promotes central nervous system-dependent release of mesenchymal stem cells. Stem Cells 2017; 35(5):1303-1315. https://doi.org/10.1002/stem.2613

Electroacupuncture (EA) performed in rats and humans using limb acupuncture sites, LI-4 and LI-11, and GV-14 and GV-20 (humans) and *Bai-hui* (rats) increased functional connectivity between the anterior hypothalamus and the amygdala and mobilized mesenchymal stem cells (MSCs) into the systemic circulation. In human subjects, the source of the MSC was found to be primarily adipose tissue, whereas in rodents the tissue sources were considered more heterogeneous. Pharmacological disinhibition of rat hypothalamus enhanced sympathetic nervous system (SNS) activation and similarly resulted in a release of MSC into the circulation. EA-mediated SNS activation was further supported by browning of white adipose tissue in rats. EA treatment of rats undergoing partial rupture of the Achilles tendon resulted in reduced mechanical hyperalgesia, increased serum interleukin-10 levels and tendon remodeling, effects blocked in propranolol-treated rodents. To distinguish the afferent role of the peripheral nervous system, phosphoinositide-interacting regulator of transient receptor potential channels (Pirt)-GCaMP3 (genetically encoded calcium sensor) mice were treated with EA acupuncture points, ST-36 and LIV-3, and GV-14 and *Bai-hui* and resulted in a rapid activation of primary sensory neurons. EA activated sensory ganglia and SNS centers to mediate the release of MSC that can enhance tissue repair, increase anti-inflammatory cytokine production and provide pronounced analgesic relief.

Longhini A, Salazar T, Vieira C et al. Peripheral blood-derived mesenchymal stem cells demonstrate immunomodulatory potential for therapeutic use in horses. PLoS One 2019; 14(3):e0212642. https://doi.org/10.1371/journal.pone.0212642

Previously, we showed that mesenchymal stem cells (MSC) can be mobilized into peripheral blood using electroacupuncture (EA) at acupoints, LI-4, LI-11, GV-14, and GV-20. The purpose of this study was to determine whether EA-mobilized MSC could be harvested and expanded in vitro to be used as an autologous cell therapy in horses. Peripheral blood mononuclear cells (PBMC) isolated from young and aged lame horses (n = 29) showed a marked enrichment for MSCs. MSC were expanded *in vitro* (n = 25) and administered intravenously at a dose of 50 × 106 (n = 24). Treatment resulted in significant improvement in lameness as assessed by the American Association of Equine Practitioners (AAEP) lameness scale (n = 23). MSCs exhibited immunomodulatory function by inhibition of lymphocyte proliferation and induction of IL-10. Intradermal testing showed no immediate or delayed immune reactions to MSC (1 × 106 to 1 × 104). In this study, we demonstrated an efficient, safe and reproducible method to mobilize and expand, *in vitro*, MSCs in sufficiently high concentrations for therapeutic administration. We confirm the immunomodulatory function of these cells *in vitro*. This non-pharmacological and non-surgical strategy for stem cell harvest has a broad range of biomedical applications and represents an improved clinically translatable and economical cell source for humans.