A Commentary on “Electroacupuncture Attenuates Ketamine-Induced Neuronal Injury in the Locus Coeruleus of Rats through Modulation of the CAMK II/CREB Pathway”

Runzhi Li1,2, Huachun Miao3, Hong Luo1,∗

1Affiliated Mental Health Center & Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou, 310007, Zhejiang, China
2The Fourth School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, 310053, Zhejiang, China
3Department of Human Anatomy, Wannan Medical College, Wuhu, 241000, Anhui, China

∗Correspondence should be addressed to Hong Luo, luohong@vip.126.com

Received date: February 07, 2024, Accepted date: February 13, 2024


Abstract

The research article entitled “Electroacupuncture (EA) attenuates ketamine-induced neuronal injury in the locus coeruleus of rats through modulation of the CAMK II/CREB pathway” makes a substantial contribution to our comprehension of the neuroprotective effects associated with EA. In this commentary, our objective is to intricately expand upon the discourse initiated by the focal article, scrutinizing recent advancements in the field and subjecting pivotal issues to critical analysis. By delving into the nuanced implications of the findings and elucidating potential trajectories for future exploration, we intend to cultivate a more profound insight into the therapeutic prowess of EA concerning ketamine-induced neuronal injury.

Keywords: Electroacupuncture, Ketamine, Locus coeruleus, CAMK II, CREB

Introduction

The focal article systematically probes the protective effects of electroacupuncture (EA) against ketamine-induced neuronal injury, elucidating the intricate involvement of the CAMK II/CREB pathway. Leveraging this foundational exploration, the present commentary endeavors to furnish a comprehensive analysis of the study's implications and discern recent advancements within the neuroprotection domain.

Recent Updates and Advances in the Neuroprotective Effects of EA

Since the publication of the focal article, there have been noteworthy developments in the study of the protective effects of EA on the nervous system. EA has great potential in neuroprotection and has been used as an important adjunctive therapy in treating various diseases.

Several studies have reported on the neuroprotective capabilities of EA, elucidating its potential to activate neuronal antioxidant functions through the p62/Keap1/Nrf2 signaling pathway. Furthermore, EA has demonstrated efficacy in inhibiting neuronal iron-induced cell death and enhancing cognitive function in mouse models of Alzheimer's disease [1]. Additionally, EA has exhibited the capacity to ameliorate neuronal damage and attenuate Parkinson's disease in mice through the TRPC1 and SIRT1/AMPK signaling pathways, mitigating mitochondrial dysfunction and alleviating symptomatic progression [2]. Notably, auricular transcutaneous vagus nerve stimulation (atVNS), akin to EA, has exhibited promise as an adjunctive therapy in opioid withdrawal treatment by targeting the locus coeruleus (LC), suggesting its potential to ameliorate withdrawal symptoms [3].

In the realm of post-stroke depression, EA treatment has proven effective in improving depressive-like behavior and enhancing mitochondrial function through the activation of AMPK in rat models [4]. Moreover, research indicates that EA can...

exert a protective effect on neurological function in cerebral ischemia/reperfusion rats by down-regulating the JAK2/STAT3 pathway, thereby alleviating neuroinflammatory responses and restoring neurological function in a post-stroke state [5]. Notably, EA at acupuncture point GB20 has demonstrated potential in ameliorating the negative cognitive effects induced by middle cerebral artery occlusion (MCAO) in rats by modulating the CACNA1B-CaM-CaMKII-CREB axis, as evidenced by increased phosphorylation of CaM, CaMKII, and CREB [6].

Furthermore, the combination of EA with medication has yielded promising outcomes, with recent research demonstrating its superiority over other therapeutic modalities, particularly medication alone, in the treatment of vascular mild cognitive impairment (VMCI). A comprehensive analysis of thirty-two randomized controlled trials showcased the superior overall efficacy of EA, either alone or in combination with medication, over medication alone, particularly in terms of cognitive function improvement. These findings underscore the considerable potential advantages offered by EA in the realm of neuroprotection [7].

Critical Analysis of the CAMK II/CREB Pathway Modulation

The focus article posited that EA elicits its neuroprotective effects through the modulation of the CAMK II/CREB pathway. This section of the commentary analyzes the evidence supporting this pathway, discussing its relevance and potential limitations. Furthermore, alternative pathways or mechanisms that could contribute to the observed neuroprotection are considered, presenting a balanced perspective on the molecular underpinnings.

The focus article underscores the association of CREB with addiction memory formation, indicating that CAMK II activation promotes CREB phosphorylation. EA treatment, as highlighted in the study, effectively reduces the expression of CaMK II and p-CREB in the LC, suggesting a potential neurobiological mechanism underlying the neuroprotective effects of EA on LC neuronal cells and the concurrent enhancement of cognitive function. However, it is notable that the potential neuroprotective mechanism of the CAMK II/CREB pathway on neuronal cells remains unelucidated in the focused article and necessitates further exploration.

In extending our understanding, EA’s ability to enhance neuroplasticity in senescence-accelerated mouse-prone 8 mice is revealed, achieved through the modulation of the Oxa-mediated cAMP/PKA/CREB signaling pathway. This modulation results in an improvement in cognitive function, suggesting the potential utility of EA in preventing and treating age-induced cognitive impairment [8]. We perceive this neurobiological foundation as crucial for modulating the CAMK II/CREB pathway to exert neuroprotective effects and anticipate more relevant studies in the future.

Currently, a burgeoning body of research is dedicated to unraveling the molecular basis of EA in the realm of neuroprotection. It is imperative to contemplate whether EA can extend its protective effects to neurons through the modulation of alternative pathways, ensuring a comprehensive and balanced perspective. In summary, a more profound and comprehensive exploration of the regulation of the CAMK II/CREB pathway is warranted to enhance our understanding of its role in neurological function and disease development. This, in turn, will facilitate the identification of more effective targets and strategies for neuroprotective therapy.

Clinical Implications and Applications

Comprehending the clinical relevance of the study is pivotal for translating laboratory findings into practical applications. This commentary aims to scrutinize the potential clinical implications of EA in treating ketamine-induced neuronal injury, contemplating its applicability to human subjects. Discussions will encompass safety considerations, feasibility, and the potential integration of EA into existing therapeutic approaches.

Ketamine, a noncompetitive antagonist targeting N-methyl-D-aspartate (NMDA) receptors, exhibits a complex mechanism of action with diverse clinical implications. While standard doses of ketamine are primarily employed for anesthesia and analgesia in surgery, recent studies have unveiled its therapeutic effects in conditions such as asthma, epilepsy, depression, bipolar disorder, and substance addiction. Despite being generally considered safe in small doses and short-term use, ketamine’s recognition as a common drug of abuse, inducing dissociative symptoms, underscores its limited clinical application [9]. Ketamine abuse poses risks of toxicity, including adverse neurocognitive effects, as evidenced by studies demonstrating locomotor excitatory and lethal effects in mice and psychosis-like neurocognitive effects in rats [10]. The focus article suggests that EA could ameliorate ketamine-induced LC neuronal damage and enhance neurobehavioral traits. Our results affirm that EA mitigates neuronal damage in the LC of ketamine-abusing rats, fostering optimism about EA’s potential to enhance the safety profile of ketamine use and broaden its clinical utility.

Acupuncture, as a modality in Chinese medicine, enjoys widespread utilization across 196 countries and regions globally [11]. EA is an integral component of traditional acupuncture involving the amalgamation of acupuncture and electrical stimulation, provides a quantifiable means of stimulation. Its widespread use in clinical practice across multiple countries attests to its efficacy. Boasting favorable electrophysiological properties, pulsed current stimulation during EA promotes blood circulation, enhances metabolism, and regulates the balance of meridians associated with acupuncture points, amplifying the circulatory effects. As an adjunctive treatment, EA demonstrates commendable...
safety, significantly enhancing clinical therapeutic outcomes while concurrently reducing the incidence of adverse drug reactions[12]. The synergistic combination of EA with antidepressant drugs not only improves therapeutic efficacy but also minimizes drug-related side effects. This synergistic approach capitalizes on the unique strengths of traditional Chinese medicine therapy, culminating in the formulation of a standardized, safe, and efficient green treatment paradigm with broad application prospects [13]. Furthermore, the cost-effectiveness of EA therapy contributes to a reduction in the medical burden on patients, curbing adverse drug effects, and further catalyzing the widespread adoption of EA therapy, thereby conferring substantial societal benefits.

**Challenges and Future Directions**

Every research endeavor encounters challenges and limitations. This section of the commentary undertakes a critical evaluation of the experimental design, methodology, and potential biases in the focal article. Subsequently, it delineates avenues for future research, emphasizing areas necessitating further exploration to corroborate and broaden the existing findings. Suggestions for refining experimental protocols or investigating diverse animal models are contemplated.

The widespread acceptance of acupuncture as a traditional treatment modality in East Asia introduces a potential source of bias in experimental studies [14]. Notably, acupoint selection and the frequency of EA represent critical sources of bias. Despite the widespread application of EA therapy in clinical practice, it encounters numerous challenges in the realm of neuroprotective therapy. Its potential in the adjudant treatment of chronic and relapsing diseases requires scrutiny, with future studies mandating substantial sample sizes and protracted follow-up periods. Exploring the optimal treatment frequency and acupoint selection for EA therapy is imperative to unravel its long-term efficacy for enhanced clinical application.

While the focus article demonstrates EA’s capacity to attenuate ketamine-induced neuronal damage and mitigate drug-related side effects as a safe treatment, future studies should consider EA as the sole intervention in Traditional Chinese Medicine. There is a pressing need to explore its conjunction with other treatments for heightened efficacy. The expansion of the clinical application spectrum of EA therapy hinges on the exploration and implementation of more combined treatment modalities, with an earnest hope that subsequent high-quality, large-sample studies will validate these perspectives.

The study in the focal article furnishes preliminary evidence for the clinical application of EA in neuroprotective therapy. The subsequent phase of the study may encompass the following dimensions: i. An objective evaluation of the precise efficacy of EA combined with medication in treating depression and other disorders, elucidating the parameters of EA, the type of medication, and the quantitative-effective relationship. This entails a focused effort to clarify the net effect of EA and its potential advantages; ii. Integration of experimental studies to unravel the possible mechanisms underpinning needle-drug combinations in neuroprotective therapy; iii. An emphasis on standardizing operational protocols and objective evaluation methods in clinical studies on EA and combination therapy, fortified by rigorous quality control measures; iv. Formulation of clinical pathways or evidence-based clinical practice guidelines for needle-drug combination therapy, offering a systematic and well-regulated framework for its application.

**Conclusion**

As we navigate the intricate landscape of EA’s neuroprotective potential, this commentary endeavors to provide a nuanced perspective on the focal article. Through the assimilation of recent updates, a critical examination of proposed mechanisms, and an exploration of broader implications, our aim is to contribute substantively to the ongoing discourse surrounding neuroprotection, fostering an environment conducive to further research in this promising domain.

**References**


7. Hou Z, Yu X, Chen J, Brenner JS, Sun Z, Shang H. Does acupuncture have advantages in the rehabilitation of vascular mild cognitive


