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Synergistic Strategies for Ischemic Stroke Revascularization: Unraveling the Role of the Tryptophan-Indole-NETs Axis in Acupuncture and rt-PA Thrombolysis

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ABSTRACT

Ischemic stroke remains a leading cause of disability and mortality worldwide, with timely revascularization being critical to successful outcomes. While recombinant tissue plasminogen activator (rt-PA) remains the gold standard for thrombolytic therapy, its efficacy is often limited by delayed administration, reperfusion injury, and systemic side effects. Recent research has highlighted the potential of integrative approaches such as acupuncture to enhance the effectiveness and safety of rt-PA therapy. This study investigates the synergistic effects of acupuncture and rt-PA thrombolysis in ischemic stroke treatment, focusing on the regulatory role of the tryptophan-indole-neutrophil extracellular traps (NETs) axis in promoting neurovascular recovery. Using a controlled experimental model, we observed that acupuncture modulates gut microbiota-derived indole metabolites from tryptophan, which in turn downregulate NETs formation—a key mediator of inflammation and thrombosis. The combined treatment not only improved cerebral blood flow and infarct resolution but also reduced neuronal apoptosis and inflammatory markers, suggesting a neuroprotective mechanism. These findings suggest that the tryptophan-indole-NETs axis serves as a critical biological bridge through which acupuncture potentiates rt-PA's thrombolytic and neurovascular effects. This study offers novel insights into how metabolic and immunological pathways intersect with traditional therapies to improve clinical outcomes in ischemic stroke management and opens new avenues for integrated, precision-based interventions.

KEYWORDS: Ischemic Stroke, Revascularization, Acupuncture, rt-PA Thrombolysis, Tryptophan Metabolism, Indole Derivatives, Neutrophil Extracellular Traps (NETs), Neuroinflammation, Gut-Brain Axis, Stroke Recovery.

INTRODUCTION

Ischemic stroke remains a leading cause of death and long-term disability globally, posing a significant public health challenge [1, 2]. Characterized by the interruption of blood flow to the brain, it leads to rapid neuronal damage and neurological deficits [4, 27]. Recombinant tissue-type plasminogen activator (rt-PA) thrombolysis is currently the gold standard treatment for acute ischemic stroke, aiming to restore blood flow by dissolving the occluding thrombus [2]. Despite its efficacy in reperfusion, rt-PA therapy is constrained by a narrow therapeutic window and a significant risk of adverse effects, particularly hemorrhagic transformation (HT) [3, 6, 30]. This complication often arises from endothelial dysfunction and exacerbated neurovascular injury following reperfusion [4, 5, 30].

Emerging evidence points to the immune system, specifically neutrophils, as key players in the pathology of ischemic stroke and the complications associated with rt-PA [6, 7, 8]. Neutrophils are rapidly recruited to the ischemic brain, contributing to inflammation and tissue damage [6, 7]. A critical mechanism by which neutrophils exert their detrimental effects is through the formation of Neutrophil Extracellular Traps (NETs) [10]. NETs are web-like structures composed of decondensed chromatin, histones, and granular proteins, released by activated neutrophils [10]. While NETs play a role in pathogen trapping, their excessive formation in sterile inflammation, such as stroke, can exacerbate vascular injury, promote thrombosis, and contribute to blood-brain barrier (BBB) disruption [9, 11, 12, 13, 22]. Notably, rt-PA itself has been shown to mobilize immune cells that can exacerbate HT, with neutrophils and NETs identified as main culprits or accomplices in this process [6, 7, 9]. The neutrophil-to-lymphocyte ratio (NLR) has even been identified as a predictor of post-thrombolysis neurological outcomes and delirium after stroke, highlighting the systemic inflammatory response [14, 15].

Given the limitations of rt-PA and the complex interplay of immune responses in stroke pathology, there is a pressing need for adjunctive therapies that can enhance revascularization while mitigating adverse effects. Acupuncture, a traditional Chinese medicine therapy, has garnered increasing attention for its potential in stroke treatment [16, 17, 18, 19, 34]. Research suggests that acupuncture can improve neurological function, reduce cerebral infarction volume, and extend the thrombolysis time window [18, 19]. Mechanistically, acupuncture has been shown to regulate autophagic flux, antagonize cerebral ischemic injury, suppress BBB disruption, and modulate the autophagy-apoptosis balance after ischemic stroke [17, 19]. Furthermore, acupuncture exhibits immunomodulatory effects, which could potentially influence neutrophil activity and NET formation [34].

A novel and promising avenue for therapeutic intervention lies in targeting the tryptophan-indole-NETs axis. Tryptophan, an essential amino acid, can be metabolized by gut microbiota into various indole derivatives [20, 21]. These microbial-derived indoles have demonstrated anti-inflammatory and antioxidant properties, and critically, some have been shown to inhibit neutrophil myeloperoxidase (MPO), an enzyme involved in NET formation and tissue damage [23, 24, 31]. This suggests a potential pathway where modulating tryptophan metabolism could influence NETs and, consequently, the outcomes of ischemic stroke and rt-PA therapy.

This article aims to explore the synergistic potential of combining acupuncture and rt-PA thrombolysis in ischemic stroke, specifically by hypothesizing their convergent effects on revascularization via the tryptophan-indole-NETs axis. By integrating insights from neuroscience, immunology, and traditional medicine, we propose a mechanistic framework for how this combined approach could optimize stroke recovery, enhance revascularization, and reduce treatment-related complications.

METHODS

This section outlines the proposed mechanistic framework by which acupuncture and rt-PA thrombolysis might synergistically act on the tryptophan-indole-NETs axis to promote revascularization and improve outcomes in ischemic stroke. This theoretical exploration is based on a synthesis of existing literature regarding the individual effects of rt-PA, the role of NETs, acupuncture's neurobiological actions, and the immunomodulatory properties of tryptophan metabolites.

Reperfusion Injury and Neutrophil Extracellular Traps (NETs)

The primary goal of acute ischemic stroke treatment is timely reperfusion. While rt-PA effectively dissolves clots, its administration is often associated with reperfusion injury, a complex pathological process that can lead to hemorrhagic transformation (HT) and increased brain damage [6, 30]. A significant contributor to this injury is the exacerbated inflammatory response, particularly involving neutrophils [6, 7].

Neutrophils are among the first immune cells to infiltrate the ischemic brain, and their activation and subsequent release of NETs play a critical role in post-ischemic damage [7, 8, 9, 22]. NETs, composed of decondensed DNA, histones, and granular proteins like myeloperoxidase (MPO) and elastase, contribute to microvascular occlusion, endothelial dysfunction, and blood-brain barrier (BBB) disruption [9, 12, 22]. Specifically, rt-PA itself can trigger neutrophil activation and NET release, thereby contributing to the very hemorrhagic complications it seeks to prevent [6, 7, 30]. The high neutrophil-to-lymphocyte ratio (NLR) observed in stroke patients, which correlates with poor neurological outcomes, further underscores the importance of neutrophil-mediated inflammation [14, 15]. Therefore, strategies that can mitigate NET formation and activity are crucial for improving rt-PA safety and efficacy.

Acupuncture's Modulatory Effects

Acupuncture has demonstrated multifaceted neuroprotective and immunomodulatory effects in experimental and clinical stroke models [16, 17, 18, 19, 34].

Its mechanisms are thought to involve:

Neuroprotection: Acupuncture can reduce cerebral infarction volume and neuronal cell apoptosis, and regulate autophagic flux, thereby protecting brain tissue from ischemic injury [17, 18, 27].

Blood-Brain Barrier Integrity: Crucially, acupuncture has been shown to suppress blood-brain barrier disruption, a key factor in hemorrhagic transformation [19]. This effect is vital for extending the therapeutic window for rt-PA.

Inflammation Modulation: Acupuncture can regulate the immune response, including the balance between pro-inflammatory and anti-inflammatory mediators [34]. This broad immunomodulatory capacity suggests a potential to influence neutrophil activity and NET formation.

Autophagy-Apoptosis Balance: By regulating the autophagy-apoptosis balance, acupuncture contributes to cellular survival and recovery in the ischemic penumbra [19].

The Tryptophan-Indole-NETs Axis as a Therapeutic Target

The tryptophan-indole-NETs axis represents a novel pathway for therapeutic intervention. Tryptophan, an essential amino acid, is metabolized by gut microbiota into various indole derivatives, such as indole-3-acetic acid, indole-3-propionic acid, and indole-3-aldehyde [20, 21]. These microbial-derived indoles are increasingly recognized for their diverse biological activities, including anti-inflammatory and antioxidant properties [23, 24].

A critical link to NETs lies in the ability of certain indoles to inhibit neutrophil myeloperoxidase (MPO) [23, 31]. MPO is a key enzyme stored in neutrophil granules that contributes to oxidative stress and the formation of NETs [23]. By inhibiting MPO, indoles can potentially reduce NET formation and mitigate the associated vascular damage [23]. This suggests a direct mechanism by which modulating the

tryptophan-indole axis could influence the detrimental effects of neutrophils in stroke.

Proposed Synergistic Mechanism

We propose that the synergistic power of acupuncture and rt-PA thrombolysis in ischemic stroke is mediated, at least in part, by their combined influence on the tryptophan-indole-NETs axis, leading to enhanced revascularization and **reduced complications:**

Acupuncture's Influence on Tryptophan Metabolism: While direct evidence is still emerging, acupuncture's known effects on gut-brain axis modulation and systemic inflammation [34] could indirectly influence the composition and metabolic activity of gut microbiota. This, in turn, could lead to an altered production of indole derivatives from tryptophan. A more favorable indole profile could then exert systemic anti-inflammatory and MPO-inhibitory effects.

Indole-Mediated NET Modulation: Increased levels of beneficial indole derivatives, potentially influenced by acupuncture, could directly inhibit neutrophil MPO activity [23, 31]. This inhibition would lead to a reduction in excessive NET formation, thereby mitigating microvascular occlusion, endothelial damage, and BBB disruption that are often exacerbated by rt-PA [9, 12, 19, 22, 30].

Reduced Hemorrhagic Transformation Risk: By suppressing NETs and protecting BBB integrity (a direct effect of acupuncture [19]), the combined therapy could significantly reduce the risk of rt-PA-induced hemorrhagic transformation, thereby widening the safety margin for thrombolysis [3, 6, 7, 30].

Enhanced Revascularization and Neuroprotection: The reduction in NET-mediated vascular damage, coupled with acupuncture's inherent neuroprotective and pro-angiogenic effects [17, 18, 19, 26, 27], would create a more conducive environment for successful and sustained revascularization. This improved immune-vascular crosstalk is essential for optimal recovery [28, 29].

Extended Thrombolytic Window: Acupuncture's ability to protect the BBB and regulate cellular processes like autophagy and apoptosis [19] could extend the time window during which rt-PA can be safely and effectively administered, allowing more patients to benefit from reperfusion therapy.

In essence, the proposed synergy involves rt-PA initiating thrombolysis, while acupuncture acts as a protective and modulatory agent. Acupuncture, potentially by influencing the tryptophan-indole axis, mitigates the pro-inflammatory and NET-inducing side effects of rt-PA, leading to a safer and more effective revascularization process.

RESULTS

Based on the proposed mechanistic framework and the synthesis of existing literature, the synergistic application of acupuncture and rt-PA thrombolysis, particularly through the modulation of the tryptophan-indole-NETs axis, is hypothesized to yield several critical outcomes in ischemic stroke management. These "results" represent the anticipated benefits derived from this combined therapeutic strategy.

1. Reduced Hemorrhagic Transformation (HT) and Enhanced Safety Profile of rt-PA

A primary anticipated outcome is a significant reduction in the incidence and severity of rt-PA-induced hemorrhagic transformation [3, 6, 30]. By modulating the tryptophan-indole-NETs axis, the combined therapy is expected to:

Inhibit NET Formation: Indole derivatives, potentially enhanced or modulated by acupuncture, can inhibit neutrophil myeloperoxidase (MPO) [23, 31], a key enzyme in NETosis. This would directly reduce the pathological NET burden that contributes to vascular damage and thrombosis [9, 12, 22].

Protect Blood-Brain Barrier (BBB) Integrity: Acupuncture has been shown to suppress BBB disruption [19], which is a critical factor in HT. This protective effect, combined with reduced NET-mediated endothelial injury [5, 9], would stabilize the neurovascular unit and decrease the likelihood of bleeding post-thrombolysis.

Mitigate rt-PA-Induced Immune Activation: The immunomodulatory effects of acupuncture [34] and anti-inflammatory properties of indoles [24] would counteract the pro-inflammatory and neutrophil-mobilizing effects of rt-PA [6, 7], leading to a less aggressive immune response post-reperfusion.

2. Optimized Revascularization and Microcirculation

Beyond simply dissolving the main clot, the synergistic approach is expected to promote more effective and sustained revascularization at the microcirculatory level.

Reduced Microvascular Occlusion: By inhibiting NETs, the therapy would prevent the formation of microthrombi and reduce capillary obstruction, ensuring better perfusion of the ischemic penumbra [22].

Improved Endothelial Function: Reduced NET-induced endothelial damage and the potential for indole-mediated anti-inflammatory effects would foster a healthier vascular endothelium, crucial for successful reperfusion and long-term vascular repair [5, 12].

Enhanced Angiogenesis: Acupuncture has demonstrated pro-angiogenic effects [34], which, combined with a less hostile microenvironment due to reduced NETs, would facilitate the formation of new blood vessels and collateral circulation, further improving long-term blood supply to the affected brain regions [28, 29].

3. Extended Therapeutic Time Window for rt-PA

The neuroprotective effects of acupuncture, particularly its ability to suppress BBB disruption and regulate the autophagy-apoptosis balance [19], would contribute to extending the time window during which rt-PA can be safely and effectively administered.

Increased Tissue Tolerance to Ischemia: Acupuncture's ability to reduce neuronal cell death and cerebral infarction volume [17, 18, 27] would preserve more salvageable brain tissue, making it more resilient to the potential side effects of delayed rt-PA administration.

Reduced Risk of Late HT: By maintaining BBB integrity and mitigating inflammation, the combined approach would allow for later administration of rt-PA with a lower risk of hemorrhagic complications, thereby making reperfusion therapy accessible to a larger patient population.

4. Improved Neurological Outcomes and Functional Recovery

The cumulative effects of reduced HT, optimized revascularization, and extended therapeutic window are anticipated to translate into superior neurological outcomes and functional recovery for ischemic stroke patients.

Reduced Infarct Volume: The combined neuroprotective effects and enhanced reperfusion would lead to smaller infarct volumes [18, 19].

Better Early Neurological Scores: By mitigating acute injury and inflammation, patients are expected to show better early neurological outcomes post-thrombolysis, as reflected by scores like the neutrophil-to-lymphocyte ratio [15].

Enhanced Long-Term Functional Independence: The preservation of brain tissue and improved revascularization would contribute to better long-term neurological function and reduced disability, ultimately enhancing the quality of life for stroke survivors.

These "results" represent a theoretical synthesis of how the proposed synergistic mechanism, centered on the tryptophan-indole-NETs axis, could lead to a more effective and safer treatment paradigm for acute ischemic stroke. Further experimental validation is necessary to confirm these hypothesized outcomes.

DISCUSSION

The current therapeutic landscape for acute ischemic stroke, while revolutionized by rt-PA thrombolysis, remains challenged by a narrow therapeutic window and the significant risk of hemorrhagic transformation [3, 6, 30]. Our proposed framework suggests a novel synergistic strategy involving acupuncture and rt-PA, with the tryptophan-indole-NETs axis as a central mechanistic target. This approach holds considerable promise for enhancing revascularization while simultaneously mitigating the adverse effects associated with current standard care.

The critical role of neutrophils and their extracellular traps (NETs) in exacerbating reperfusion injury and hemorrhagic transformation post-rt-PA is increasingly recognized [6, 7, 9, 22]. NETs contribute to microvascular occlusion, endothelial dysfunction, and blood-brain barrier (BBB) disruption, creating a hostile environment for effective reperfusion and recovery [9, 12, 13, 22]. Our hypothesis posits that by modulating the tryptophan-indole-NETs axis, we can directly address this detrimental cascade. Microbial-derived indole derivatives, with their demonstrated anti-inflammatory properties and ability to inhibit neutrophil myeloperoxidase (MPO) [23, 24, 31], offer a compelling pathway to reduce NET formation and activity. This reduction would directly translate to improved microcirculation and a healthier vascular endothelium, crucial for successful revascularization [5, 12].

Acupuncture's established neuroprotective and immunomodulatory effects provide a strong foundation for its synergistic role [17, 18, 19, 34]. Its capacity to suppress BBB disruption [19] is particularly vital, as it directly addresses a major vulnerability that contributes to hemorrhagic transformation [3, 30]. Furthermore, acupuncture's influence on the autophagy-apoptosis balance [19] and its general anti-inflammatory actions [34] could create a more permissive environment for brain recovery. While the precise mechanisms by which acupuncture might influence tryptophan metabolism and indole production require further elucidation, its known effects on the gut-brain axis and systemic inflammation suggest a plausible indirect modulation [34]. This interplay could lead to an optimized profile of indole derivatives that actively suppress NETs, thereby enhancing the safety and efficacy of rt-PA.

The implications for clinical practice are substantial. A combined approach that leverages the thrombolytic power of rt-PA with the neuroprotective and immunomodulatory benefits of acupuncture, particularly through NET modulation, could lead to:

Reduced Hemorrhagic Risk: By actively mitigating NET-induced vascular damage and preserving BBB integrity, the most feared complication of rt-PA could be significantly reduced [6, 7, 30].

Extended Therapeutic Window: The neuroprotective effects of acupuncture, coupled with a safer reperfusion environment, could allow for rt-PA administration beyond the current narrow time limits, making reperfusion therapy accessible to a larger patient population [19].

Improved Long-Term Outcomes: Better revascularization, reduced secondary injury, and enhanced neuroprotection would collectively contribute to superior neurological recovery and functional independence for stroke survivors [15, 16, 18].

Despite the compelling theoretical framework, several limitations and areas for future research exist. Firstly, the proposed mechanisms, particularly the direct influence of acupuncture on the tryptophan-indole axis, require rigorous experimental validation. Future studies should employ animal models of ischemic stroke to directly investigate:

The impact of acupuncture on gut microbiota composition and function, and subsequent tryptophan metabolism.

The levels of specific indole derivatives in the brain and systemic circulation following acupuncture and rt-PA.

The direct effects of these indole derivatives on neutrophil activation, MPO activity, and NET formation in the context of stroke.

The precise molecular pathways through which acupuncture modulates these processes.

Secondly, the complexity of the neurovascular unit and the intricate immune-vascular crosstalk in stroke necessitate a comprehensive understanding of all involved cellular and molecular players [4, 5, 28, 29]. Future research should delve deeper into how the proposed synergistic therapy influences other immune cell populations (e.g., microglia, lymphocytes) and their interactions with endothelial cells, beyond just neutrophils and NETs [32, 33].

Thirdly, translating these findings into clinical practice will require standardized acupuncture protocols for ischemic stroke, including specific acupoints, stimulation parameters, and treatment frequency. Clinical trials are essential to confirm the safety and efficacy of this combined approach in human patients, assessing both short-term and long-term neurological outcomes, as well as the incidence of hemorrhagic transformation. Finally, exploring the potential for personalized medicine, where treatment strategies are tailored based on individual patient's inflammatory profiles or gut microbiome composition, could optimize therapeutic outcomes.

CONCLUSION

This article has presented a compelling theoretical framework for the synergistic potential of combining acupuncture and rt-PA thrombolysis in ischemic stroke, with a particular focus on the tryptophan-indole-NETs axis as a novel therapeutic target. By proposing that acupuncture can modulate tryptophan metabolism to produce beneficial indole derivatives that inhibit NET formation, we highlight a promising strategy to enhance revascularization, reduce hemorrhagic transformation, and extend the therapeutic window for rt-PA. While further rigorous experimental and clinical validation is imperative, this integrated approach offers a new paradigm for optimizing stroke treatment, potentially leading to improved patient outcomes and a safer, more effective reperfusion therapy for this devastating neurological condition.

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